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OBSERVATIONS ON THE MORPHOLOGY AND FUNCTIONS OF SOME OF THE COMPONENTS OF THE CORONARY CIRCUIT[1]

JOSEPH T. WEARN, M.D.

(From the Department of Medicine, Lakeside Hospital and Western Reserve University, Cleveland)

It was with much humility and great appreciation that I accepted the invitation to give the Thayer Lectures. It is an outstanding honor, not only to me, but to the many younger associates who have worked in my laboratory during the past ten years. I feel it a particular pleasure to take part in a lectureship instituted originally to honor Dr. Thayer, and which now serves as a tribute to his memory.

When one comes to study the coronary circulation he is confronted with special difficulties created by the behavior of the heart. The circulation in skeletal muscle, as shown by Krogh (1), lends itself to direct microscopic observation. Richards and Schmidt (2) utilized the method of studying the behavior of the glomeruli in the kidney, and the behavior of the vessels in the skin has been described by Dr. James Bordley (3) in this school. The lung (4) and pial vessels (5) also lend themselves very nicely to microscopic observation. Thus far, however, it has not been possible to visualize the circulation in the heart walls, in the first place, because of the motion of the heart, and in the second place, because of the unusual complexity of the coronary circulation.

In view of this complexity of the myocardial vessels it is perhaps best to begin with a description of the various component parts that make up the circuit, more or less in the order of their discovery. One of the earliest descriptions of the arteries of the heart is that of Galen (6), who gave them the name coronary. Of their structure and

[1] Lecture I of the thirteenth course of lectures under the William Sidney Thayer and Susan Read Thayer Lectureship in clinical medicine. Delivered at The Johns Hopkins School of Medicine, March 26, 1941.

function, however, he had little knowledge, for he believed that the arteries terminated as nerves.

Probably one of the first to portray the coronary arteries was that man of many interests, Leonardo da Vinci (7). In the early 16th century he made some very interesting sketches of the coronary arteries, veins, and coronary sinus, and studied in detail the origins of arteries by dissecting away the pulmonary artery. His drawings are more accurate than many of those of the anatomists who followed him. Vesalius (8) shows several plates of the coronary vessels including a view of the ostia from the aortic side, but his plates give a rather primitive idea of the coronary vessels. Other early illustrations, such as those of Bartholinus (9), in 1641, and Bidloo (10), in 1685, were also rather inaccurate. William Harvey (11), however, as shown in the text of *De Motu Cordis*, in 1649, had a very clear idea of the function of the coronary arteries. A little later, in 1671, Richard Lower (12) described quite accurately the distribution and branches of these arteries, and was the first to demonstrate the anastomoses between the two main arteries. Frederick Ruysch (13), in 1704, introduced the corrosion method in studying the finer arterial branches in the myocardium. At about the same time (1715) Raymond Vieussens (14), Professor of Medicine at Montpelier, published the results of his careful studies of the blood vessels in the heart. His dissections were meticulous, showing the circular course of the muscle fibres, and in more accurate detail the branches of the arteries. This keen observer, moreover, discovered a new group of vessels (15). Noting that clots of blood in the heart chambers gave off small tendrils which disappeared into small openings in the heart walls, he demonstrated, by the injection of saffron into the arteries, that the dye escaped through these small openings in the walls. Two years later (1708) Thebesius (16) discovered another group of vessels. By blowing air into the coronary veins with the heart immersed in water, he saw bubbles escape from the openings in the heart walls. These vessels now bear his name—thebesian veins. Thebesius was aware of Vieussen's work, and thought he had confirmed Vieussens' findings, but, as a matter of fact, they were dealing with two distinct sets of vessels. Thebesius also made an accurate guess as to the function of these veins. In 1798 John Abernethy (17) confirmed Vieussens' findings and showed, by injecting glue and other substances too thick to

penetrate capillaries, that the luminal vessels permitted their passage without difficulty.

In 1933, in collaboration with S. R. Mettier, T. G. Klumpp, and L. J. Zschiesche (18) it was shown that two distinct types of vessels connected the coronary arterioles with the chambers of the heart; one branched off directly from the arterioles and, losing its muscle wall, emptied through openings in the heart wall into the chambers. The second, after branching off the arteriolar trunks, broke up into channels with lumens of irregular diameter and with walls similar in structure to those of the capillaries. These vessels with simple endothelial linings open through the heart walls into the chambers. They are identical in structure with the sinusoids which have been described by Minot (19). The arterio-luminal vessels are not numerous, but the arterio-sinusoidal vessels are very numerous and can be readily identified in human hearts. Both types of vessels anastomose freely with capillaries.

Thebesian veins have been shown by Wearn (20), and by Grant and Viko (21) to communicate freely with the capillaries, with the coronary veins, and with one another—all of these connections being on the venous side of the capillary bed.

Another group of branches of the coronary arteries is worthy of attention. Shortly after emerging from the aorta the main trunks give off small branches which find their way to and along the great vessels, leaving the heart to anastomose with arterioles in the mediastinum, pericardium, oesophagus, trachea, lungs, upper and lower surface of the diaphragm, and in the aortic wall down as far as the abdominal cavity. These vessels were first described by Albrecht von Haller (22) in 1803, and their extensive distribution was demonstrated in our laboratory in work with C. L. Hudson and A. R. Moritz (23), in 1932.

The capillaries of the myocardium, invisible in ordinary histological sections of heart muscle can be rendered visible by injecting them with a dye (24). There is approximately one capillary to each muscle fiber in human hearts, as in the hearts of dogs, cats and rabbits. The capillaries, moreover, communicate freely with the sinusoids and the thebesian veins, so that from the anatomical viewpoint they are readily accessible to the blood in the chambers of the heart.

With all the branches of the coronary arteries, both extra- and

intracardiac, it is obvious that the system is a very complex one. The diagram (Fig. 1) shows not only the branches of the arteries, but the intricate anastomoses of the various groups of vessels with one another.

The heart, therefore, is safeguarded by many potential sources of supply of blood: (1) from the coronary arteries, (2) from the extracardiac branches, (3) from the luminal vessels on the arterial side of the capillaries, and (4) from the thebesian veins. Moreover, the

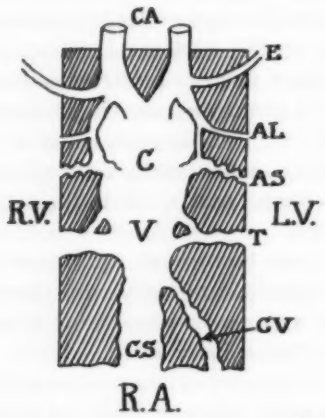

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FIG. 1. DIAGRAM SHOWING WHICH ANASTOMOSES OF VARIOUS GROUPS OF VESSELS IN THE HEART

CA = coronary arteries. C = capillaries. V = coronary veins. CS = coronary sinus. E = extracardiac branches. AL = arterio-luminal vessels. AS = arterio-sinusoidal vessels. T = Thebesian vein. CV = coronary vein. R.V. = right ventricle. L.V. = left ventricle. R.A. = right auricle.

studies of Spalteholz (25) and Gross (26) have shown that the coronary arteries anastomose with one another.

In view of all these apparent safeguards of the blood supply to the myocardium one may well ask why the occlusion of a small branch of a coronary artery results in an infarct, and frequently in death. Why do the anastomoses not function in such an emergency?

A great deal of work has been done which in my opinion furnishes the answer to this question. Spalteholz (25) and later Gross (26)

injected the coronary arteries with opaque masses and demonstrated definite anastomoses between the two coronary arteries. Others using similar methods have confirmed their findings. Injection masses, however, when forced in under high pressures in dead hearts meet little resistance and penetrate the very small arterioles, and the vessels are distended by the pressure within them. The communicating arterioles shown by Spalteholz and Gross represent the finest arterioles and do not give a true picture of these vessels during life. In the anatomical sense, therefore, the coronary arteries are not end arteries, but from the overwhelming experience of the clinician and the pathologist their behavior is that of end arteries.

There is undoubtedly considerable variation in the number and size of anastomoses between the two coronary arteries in normal hearts, as shown by Mautz and Beck (27) and others, but even in those hearts most richly supplied, the connecting channels are small and are important only as a potential source of blood.

Mautz and Beck have studied the role of the inter-arterial anastomoses in dogs during the several months following the ligation of a branch of one coronary artery. They found that the inter-arterial communications had enlarged considerably; indeed, in some instances the increase in diameter of the vessels was ten-fold that found in control animals. It is of interest that these vessels, during the months of their gradual dilatation, had not acquired a thick arterial coat, but resembled a dilated, thin-walled arteriole. All of these vessels increased in length, as shown by the striking tortuosity in each instance.

Schlesinger (28) has observed the development of similar collaterals in human hearts, but in most instances the collaterals were smaller in size. The hearts studied by him were for the most part from elderly people, while the dogs of Mautz and Beck were in many instances younger animals. The influence of age upon the response of collaterals deserves further attention.

Recently, in our laboratory[2] Drs. Eckstein, Pritchard and Gregg (29) studied the collateral branches of the femoral, carotid, and coronary arteries. The method employed consisted of ligation of these arteries

[2] This work and all the work carried on in the Department of Medicine of Western Reserve University during the past two years which is reported upon in this lecture was made possible by a generous grant from the Commonwealth Fund.

and measuring the time required for the pulse, the retrograde blood pressure, and the retrograde flow of blood to re-establish themselves at or near the control levels originally determined.

The retrograde pressures and flows in the carotid and femoral artery were measured by means of cannulae, either in the main artery or in a side branch peripheral to the ligation. Immediately after occlusion of the femoral artery the retrograde pressure and flow drop to a very low value and the pulse disappears. Within thirty seconds to a minute the flow, pressure, and pulse begin to return, rise rapidly for an hour, and continue to rise more slowly for the following days and weeks. Following ligation of the carotid artery the pulsation does not cease. The retrograde flow and pressure do not drop as low as they do in the femoral artery, and begin a recovery within a few seconds, which continues as in the femoral artery, but reaches its maximum more quickly.

The behavior of the collaterals of the coronary artery following ligation is in contrast to that of the femoral and carotid arteries. The initial increase in flow and pressure is very small and much slower than in the other collaterals. There may be a slight, gradual increase during the first hour, with further slow increase during the next 48 hours. Gradual augmentation of the pressure and flow occurs during the following weeks, but contraction of the muscle in the area supplied by the occluded vessel rarely begins before seven weeks.

The results of these experiments throw new light upon the behavior of the collateral circulation of the coronary arteries, for they emphasize the importance of the element of time. Whereas the collaterals of the femoral and carotid arteries may begin to function within seconds, those of the coronaries begin to function within hours, and require weeks before they become effective. These results are in agreement with those of Mautz and Beck, who found that the arteriolar anastomoses between the two coronary arteries require weeks in which to enlarge sufficiently to become effective.

The importance of the time element necessary for the arterial collaterals in the coronary circuit to adapt themselves to the demands upon them is clearly brought out by these experiments. One fact established by them also has direct clinical application—the weeks necessary for the establishment of the proper function of the

coronary collaterals should serve as a guide for the rest period necessary for those patients whose coronary arteries become occluded.

Another type of closure of the coronary arteries is that which occurs at the orifices as a result of syphilitic aortitis or advanced arteriosclerosis. In such cases complete occlusion of the ostia of both coronary arteries has been shown to be compatible with an active life (30). It should be emphasized that the processes causing such occlusions require considerable time in developing and would, therefore, give the collateral circulation, whatever its source, sufficient time to take over the new function. In such gradual occlusions of both ostia, infarction of the myocardium rarely occurs. When, however, both ostia of the coronary arteries become occluded, two obvious sources of blood supply exist—the extracardiac branches and the luminal vessels—but there is no evidence to date as to whether one or both of these sources are utilized.

The diameter of the aggregate channel of the luminal vessels is of considerable size, as shown by the fact that if the coronary arteries of a dead heart are perfused 70–80 per cent of the perfusate escapes directly into the heart chambers, with only 20–30 per cent returning by way of the coronary veins (20). The role that these vessels play in the circulation of the normal heart is still uncertain. Starling and his co-workers and pupils (31, 32, 33) assumed the flow from the luminal vessels to be constant at about 40 per cent of the inflow of the coronary arteries. They did not record the pressures in the heart chambers nor did they consider the possibility of changes of flow resulting from changes in the pressure gradients in the chambers.

Stella (34) found no flow from the peripheral ends when he cut the coronary arteries, but this procedure resulted in the death of his animals, so that at the time of his observations they were moribund.

The work of Bohning, Jochim and Katz (35) suggests that blood does enter the luminal vessels from the heart chambers. They failed to record the pressure in the right ventricle, a knowledge of which is necessary in order to evaluate their experiments.

If one considers the relationship of pressures existent in the chambers and arteries of the heart, as was done by Wiggers (36), one can arrive at certain theoretical possibilities as to the direction of flow in the luminal vessels and extracardiac anastomoses. In the normal heart

the pressures are ideal for flow from the arteries into the right ventricle and auricles during the greater part of the cardiac cycle, and for part of the cycle into the left ventricle. The almost identical pressures in the coronary arteries and extracardiac branches would prevent any flow between them at any time in the cycle. If the ostia of the coronary arteries are occluded, however, the pressure relationships are such that flow could take place from the chambers of the heart into the luminal vessels.

In recent work in our laboratory, with Drs. Eckstein, Roberts and Gregg, some evidence has been obtained concerning the role of the luminal vessels in the right ventricle. With the pressures in the right and left ventricle carefully controlled, dyes were injected into the right ventricle. A shunting device which prevented the dye from reaching the left side of the heart was placed in the pulmonary artery. Under these conditions the dye injected into the right ventricle did not enter the luminal vessels so long as the pressure in the right ventricle did not equal or exceed that in the left ventricle. In several of the hearts a few surface capillaries in the septum contained dye, but the arteries, veins, and capillary bed contained none. When similar injections were carried out while the pressure in the right ventricle was greater than that in the left, the dye entered the luminal vessels and filled the capillary bed. The pressure gradient between the left and right ventricle determines the direction of flow in the luminal vessels in the right ventricle, but under normal pressures the direction of flow is from the luminal vessels into the right ventricular cavity.

With Dr. R. E. Shipley a method has been devised for the purpose of determining the direction of flow in the luminal vessels in the different chambers of the heart. This method consists of injecting living bacteria into the left ventricle and aorta and of detecting the time of their arrival in the various heart cavities and the coronary sinus. Samples of blood are collected from these places simultaneously in small test tubes filled with the proper bacterial media, and these are arranged in a parallel position on a rotating kymograph drum. With the aid of a timing device, the time elapsing between the time of injection of the living bacteria into the left ventricle and their arrival in the culture tubes is recorded.

While this work is still in a preliminary stage, evidence is accumulat-

ing which indicates that the pressure gradients existing in the peripheral coronary arterial circulation and within the chambers control the direction and amount of flow in the luminal vessels. In a few experiments the time required for blood to pass from the left ventricle to the right ventricle was approximately one second.

Factors influencing the volume and distribution of coronary blood flow are as yet imperfectly understood. Krogh (1) has demonstrated the intermittence of blood flow in the smaller vessels in skeletal muscle. Richards and Schmidt (2) observed an intermittence of flow in the frog's glomeruli, and Bordley, Grow and Sherman (3) have observed an intermittent flow in the capillaries of the skin. Pulmonary vessels behave similarly. In our laboratory during the past ten years numerous attempts have been made to get evidence of intermittent flow in the heart. To date, however, the evidence from injection experiments in living hearts indicates that the heart utilizes all of its capillaries at all times. The slowly beating heart and the rapidly driven heart under increased load, when injected with a dye, usually show a complete injection of all available capillaries. These experiments, which are still in progress, are by no means final, but the results so far suggest that intermittence of flow does not occur in the coronary circuit.

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ALTERATIONS IN THE HEART ACCOMPANYING GROWTH AND HYPERTROPHY[1]

JOSEPH T. WEARN, M.D.

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The blood supply to the heart must necessarily be an efficient and rapidly adaptable one, in order to meet the various long-continued work loads or sudden strains that are thrown upon it in childhood during the period of growth, and in adult life.

During normal growth the heart undergoes a number of important changes in a most orderly manner. Gross (1) has shown that as the muscle mass increases the arteries increase in size and length and become more tortuous in their course. More recently, Ehrich, de la Chapelle, and Cohn (2) found that the arteries of each of the ventricles increase in direct proportion to the weight of the ventricle.

The change in the total muscle mass during growth can be best understood, perhaps, by observing the changes in the individual myocardial fibers. In work in our laboratory with Dr. R. A. Shipley and L. J. Shipley (3) we found that at the time of birth the muscle fibers of the rabbit's heart are very small, with a cross-sectional diameter of approximately 7 μ, and, since the circumference of the young rabbit's heart is small, the heart fibers are short. During growth the length increases and the cross-sectional diameter becomes greater. This process is a continuous one until adult life is reached, at which time the diameter of the fibers averages about 21 μ, where it remains throughout the life of the rabbit. The process in the human heart is similar, as shown by more recent work of Roberts and Wearn (4). In the human heart the diameter of the muscle fiber is approximately 7 μ at birth and with growth increases gradually until it reaches 14 μ, where it remains throughout adult life. The increase in the

[1] Lecture II of the thirteenth course of lectures under the William Sydney Thayer and Susan Read Thayer Lectureship in clinical medicine. Delivered at The Johns Hopkins School of Medicine, March 27, 1941.

heart weight is in direct proportion to the increase in the average diameter of the muscle fiber (Fig. 1).

In order to observe and measure the quantitative changes in the concentration of capillaries it is important that a complete injection of the capillaries be made. The most dependable method for accomplishing this result is to inject dye into the coronary arteries of

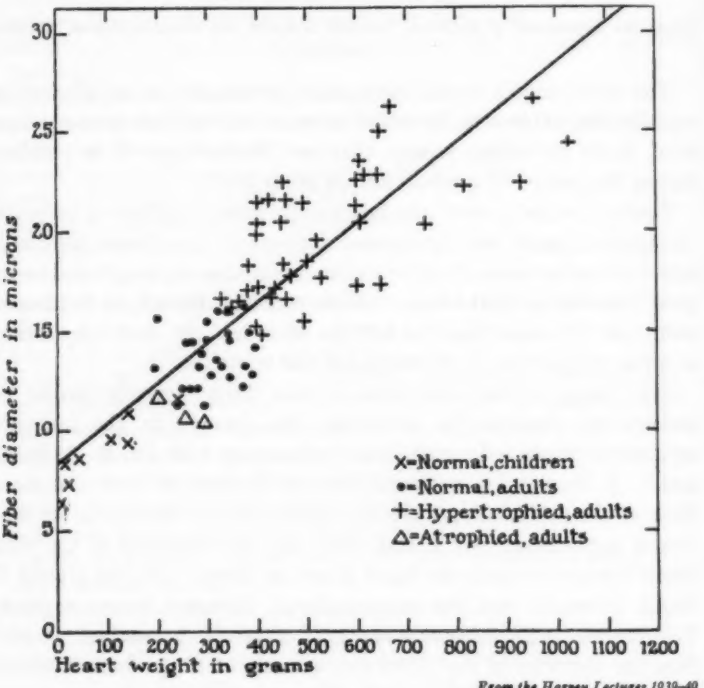

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FIG. 1. RELATIONSHIP OF FIBER DIAMETER TO HEART WEIGHT

a revived beating heart. Sections of the heart are then fixed, stained, and mounted in such a manner that shrinkage is avoided (3).

FIBER-CAPILLARY RATIO

The capillaries are distributed evenly throughout the muscle bundles, lying alongside and parallel to the fibers. In the newborn

rabbit's heart there are six muscle fibers to each capillary, while in the human heart shortly after birth (three weeks) the ratio is four fibers to one capillary. As the muscle fibers enlarge a change in the ratio results, so that by the time the rabbit is approaching adult life and the child is 15 years old there are two fibers to each capillary. When growth is completed the ratio is approximately 1:1, and it

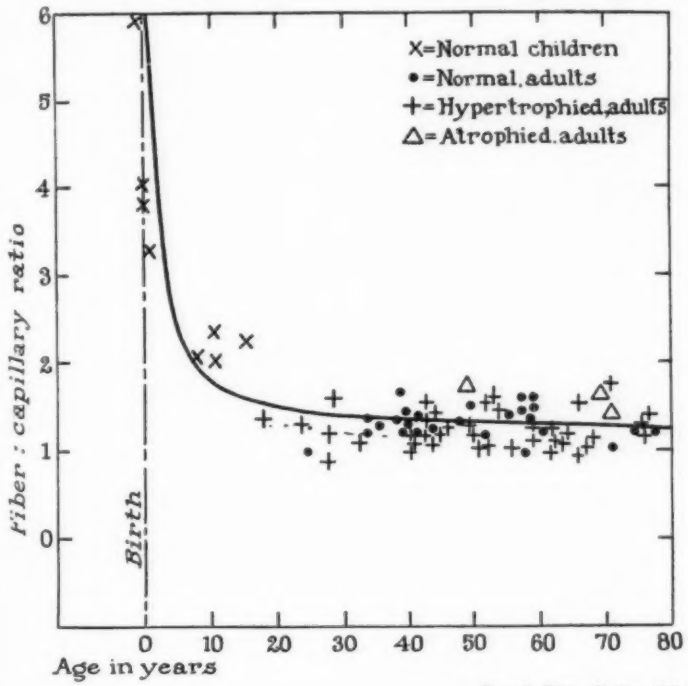

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FIG. 2. CHANGES IN FIBER-CAPILLARY RATIO WITH AGE

remains at this figure throughout adult life. The range of the F:C ratio during adult life is 0.97 to 1.68, with an average ratio of 1.34 (± 0.023). The surprising constancy of this figure during adult life is in contrast to the steadily changing one during growth. Both the human and the rabbit hearts show the same changes in the fiber-capillary ratio during growth, and curves plotted from these data are

hyperbolic in form, resembling other growth curves. Figure 2 shows the changes in the F:C ratio during growth.

Observations were also made upon the changes in the capillary bed during growth. In the rabbit at birth we found the concentration of capillaries to be about 3200 per square millimeter of muscle. The same concentration was maintained throughout the period of growth, and indeed, throughout the adult life of the rabbit, so long as the heart remained normal in size. In human hearts the concentration of

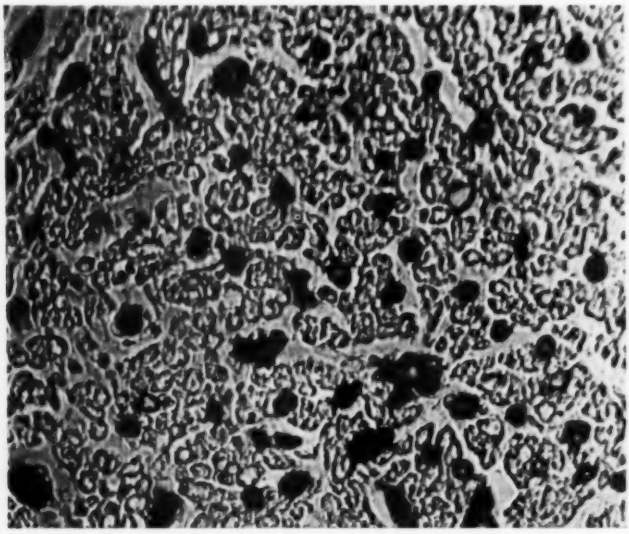

FIG. 3. HEART OF INFANT SHOWING SMALL MUSCLE FIBERS

capillaries at birth was about 3300 per square millimeter, and approximately this same concentration was found throughout physiological growth, the average for the group of 8 children's hearts being 3743 capillaries per square millimeter. Further study of the hearts of normal adults revealed that the capillary concentration remained remarkably constant throughout adult life, the range being 2993 to 4066, with a mean of 3342 ($\pm$ 40). The constancy of this figure is surprising when one considers that the range is from birth to 77

years. Also, in the rabbit, the cross-sectional area of an average fiber increased seven fold from birth to maturity. Changes of similar magnitude took place in the human hearts.

If the muscle fibers increase so greatly in area one would expect a corresponding decrease in the capillaries, but if the muscle fibers increase in diameter and the F:C ratio decreases concomitantly, while the concentration of capillaries remains constant, it follows that the

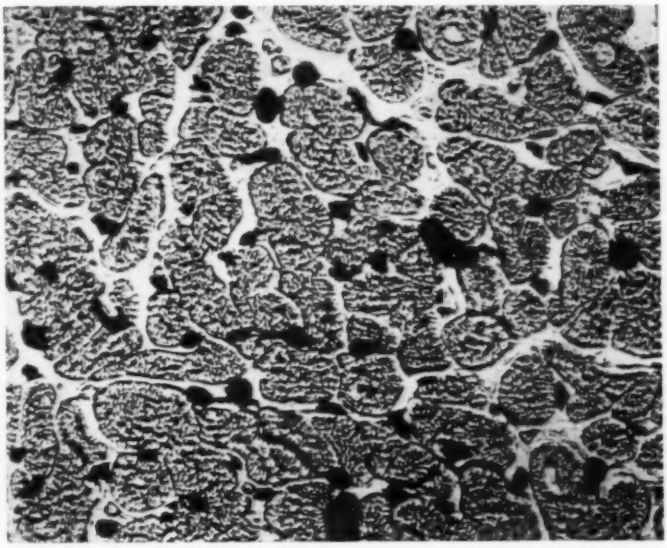

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FIG. 4. NORMAL HUMAN HEART

capillaries must multiply in number in order to maintain the constant concentration in the growing muscle mass. In normal growth of the heart, therefore, the muscle fibers increase in diameter and length and the capillaries multiply at such a rate as to maintain a constant concentration of capillaries in the muscle at all times. After growth is completed the fiber size, the F:C ratio and the concentration of capillaries remain constant so long as the heart remains normal.

HYPERTROPHY

It is common experience that in practically all instances where death results from heart failure the heart is hypertrophied. The most common exceptions, of course, are those hearts with coronary artery disease and occlusion. The belief that hypertrophy is a compensatory mechanism which enables the heart to perform more efficiently, does not rest on a factual basis. There is, indeed, no evidence that suggests that an enlarged heart is a better performer than a heart of normal

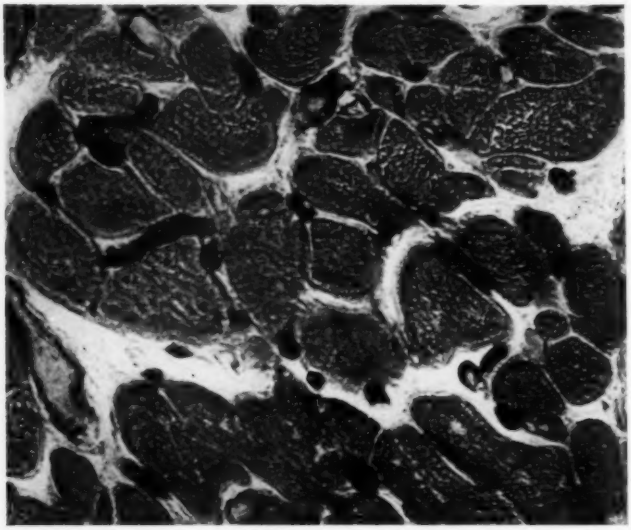

FIG. 5. HUMAN HEART SHOWING HYPERTROPHY OF MUSCLE FIBERS

size. It is even conceivable that excessive hypertrophy *per se* may lead to inefficiency of the muscle. If, for instance, during the process of hypertrophy the muscle mass should increase without a corresponding multiplication of capillaries such as occurs in normal growth, the actual concentration of capillaries would decrease. The enlargement of the individual muscle fibers would push the capillaries farther apart and thus increase the distance necessary for the oxygen to travel from the capillary to the periphery of its zone of supply.

In order to find out whether hypertrophy is accompanied by an increase in capillaries, a group of hypertrophied hearts were studied. The causes of hypertrophy were hypertension, rheumatic fever, syphilis, and arteriosclerosis of the coronary arteries. Death resulted in the majority of instances from heart failure.

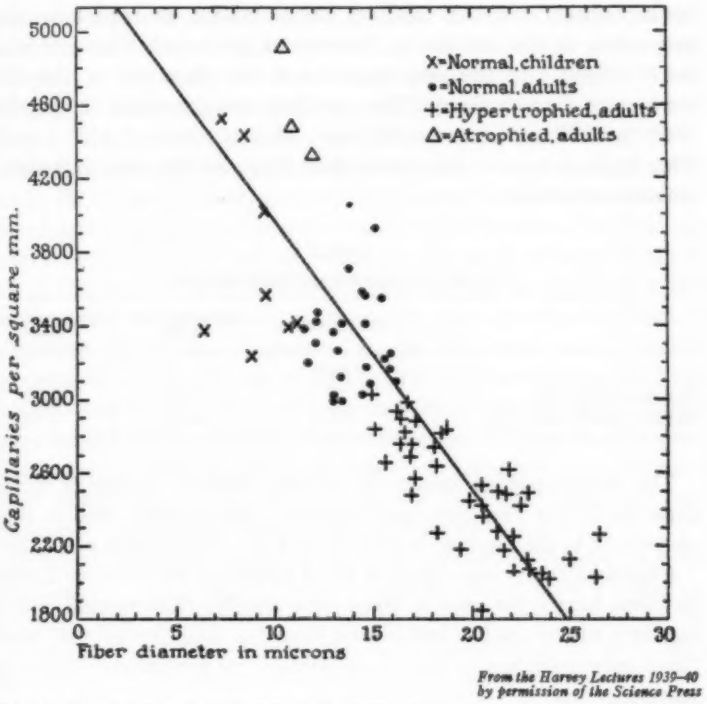

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FIG. 6. RELATIONSHIP OF CAPILLARY CONCENTRATION TO FIBER DIAMETER

The average weight of the hypertrophied hearts was 538 gm. The muscle fibers were enlarged, and this enlargement varied directly with the weight of the heart. The average muscle fiber diameter ranged from 15 μ to 26.5 μ, with a mean of approximately 20 μ, as compared to the mean of 14 μ for normal heart fibers.

The average number of fibers supplied by a capillary was 1.24,

or essentially the same as that found in normal adult hearts. This F:C ratio was also remarkably constant for all hypertrophied hearts, as it was in normal hearts of adults.

The concentration of capillaries, however, showed a definite decrease, which was clearly caused by the enlargement of the muscle fibers (Fig. 6). As the fibers enlarged the capillaries were pushed farther apart, and the capillary concentration decreased in direct proportion to the increase in diameter of the muscle fiber and in the heart weight. In the very large heart the diameters of the fibers were more than doubled. The capillary concentration ranged from 1868 to 3037 per square millimeter, with a mean of 2483 (± 31). This figure is appreciably lower than those for the normal hearts of children or adults.

TABLE I

Normal and hypertrophied hearts in rabbits

	FIBER DIAMETER	CAPILLARIES PER SQ. MM.	FIBER-CAPILLARY RATIO
	micra		
Normal hearts (15)	19.0	3420	1.14
Hypertrophied hearts (18)	22.2	2670	1.16

The hypertrophied hearts in rabbits likewise showed a definite decrease in the capillary concentration, which again was in direct proportion to the increase in fiber diameter. This is shown in Table I.

Cardiac atrophy was found in three patients with wasting diseases. In these hearts the muscle fibers were smaller than normal and the capillary concentration was greater than the figure for normal hearts. Since only three hearts have been studied, no general conclusions are justified.

The data bearing upon the growth of muscle fibers, the fiber-capillary ratio, and the capillary concentration show that a definite correlation exists. Indeed, if the fiber diameter is known the capillary concentration can be calculated, and if the heart weight is known the fiber diameter can be calculated. Likewise, a close correlation exists between the heart weight and the capillary concentration.

Hypertrophy, then, differs from normal growth in that in the latter

the capillaries multiply to keep pace with the muscle during growth, while in hypertrophy there is an actual decrease in the capillaries per unit of muscle.

MYOGLOBIN[2]

The pigment, muscle hemoglobin, or myoglobin, has been shown to possess a greater affinity for oxygen than blood hemoglobin, and it is now accepted that myoglobin plays a part in the transfer and storage of oxygen in the heart muscle. In dogs, according to Woodruff and Whipple (5) the myoglobin of the myocardium increases during normal growth. Hurtado (6) has observed that myoglobin increases in the hearts of dogs kept at high altitudes. In work in our laboratory with Dr. G. H. Hitchings, determinations of myoglobin have been made in normal and hypertrophied hearts of rabbits and of man. Our findings thus far suggest that in human hearts there is no significant change in the percentage of myoglobin as a result of hypertrophy. In a few instances the concentration of myoglobin was actually decreased in hypertrophied hearts. Moreover, in several hearts with marked hypertrophy of one side, the hypertrophied side showed less myoglobin than the smaller chambers. The average for the two groups of normal and enlarged hearts showed little difference. Technical difficulties in the method seem greater with human hearts than in analyses of rabbit hearts, because of the large amount of blood hemoglobin that remains in the muscle. The work is still under way.

In rabbit hearts myoglobin is being determined at various stages of hypertrophy. The data obtained thus far show that myoglobin, like the other intracellular constituents, is synthesized slowly as hypertrophy begins. After the process of hypertrophy is well under way the myoglobin content is approximately normal.

These findings and those of Cowan and Bauguess (7), who found no increase in myoglobin in hypertrophied hearts of rats, bring out another difference between hypertrophy and growth. If hypertrophy is a compensatory process one would expect an increase in myoglobin to accompany it.

[2] This work, reported on this and succeeding pages, was aided by a grant from the Commonwealth Fund.

ELECTROLYTE DISTRIBUTION

Changes in the distribution of electrolytes in a tissue have been shown to occur during growth. In the recent work of Hastings and Blumgart (8) shifts in electrolyte pattern were found to be a sensitive index of tissue change. In their experiments, following ligation of the coronary artery for periods too brief to give either electrocardiographic or histological evidence of damage, the electrolyte pattern showed definite changes.

In work with Dr. G. H. Hitchings the method has been employed in studying the changes during the hypertrophy which occurs in rabbit hearts following destruction of a cusp of the aortic valve. Following the production of aortic insufficiency the heart not infrequently shows considerable enlargement within the first three days. In this period the myocardium takes up considerable quantities of extracellular electrolytes and water, which probably represents an increase in interstitial fluid, although other explanations are possible. This is usually a transient phase, for within two or three days the extracellular phase returns to an approximately normal level. As the muscle hypertrophies the intracellular phase increases at a slow, and in the early stages, a constant rate.

As hypertrophy continues the proportion of extracellular fluids decreases to a point slightly below normal. Inasmuch as the extracellular fluid is probably part of the transport system from the capillary wall to the cell, its decrease may interfere with the exchange of metabolites.

Katz and Long (9) and Wiggers (10) have shown that heart muscle is incapable of establishing an oxygen debt. Diminution of the oxygen supply to the heart muscle is reflected within a few seconds in the weakened heart beat. This is in contrast to the behavior of skeletal muscle which can carry a considerable oxygen debt without harm to itself. Hastings and Blumgart (8) have shown that brief periods of anoxemia, which show no changes by biological methods, produce measurable chemical changes in the muscle. Likewise, the heart muscle tolerates much less lactic acid than skeletal muscle and depends upon its oxygen supply to remove it.

In work with Drs. J. W. Price and D. E. Gregg, oxygen utilization in the normally beating heart of the dog is being determined. With

the animal anesthetized, blood samples are collected from the left ventricle and the coronary veins as nearly simultaneously as possible. Blood from the femoral vein is also taken for comparison.

These results indicate that the heart utilizes a surprisingly large percentage of the available oxygen, even with the animal anesthetized, and therefore at complete rest. The percentage saturation of the venous blood is uniformly low, the average figure being 23 per cent, whereas the average saturation of the blood from the femoral vein is 70 per cent.

There are several observations in the literature upon the oxygen utilization of skeletal muscle during vigorous exercise. Barcroft and Kato (11), in 1915, and Himwich and Castle (12), in 1927, determined the oxygen utilization in the gastrocnemius muscles of dogs during rest

TABLE II

Percentage O_2 saturation

	ARTERIAL	VENOUS	
Himwich and Castle	92–108 av. 99	12–64 av. 38	Gastrocnemius exercised
Barcroft and Kato		51–70	Gastrocnemius exercised
Price, Wearn, and Gregg	79–97	12–53 av. 23	Heart with dog anesthetized and at rest

and during strenuous exercise. A comparison of their results with those obtained by us in the heart are shown in Table II.

This low average figure of 23 per cent O_2 saturation for coronary venous blood has been obtained repeatedly, and indicates a pretty complete use of available oxygen by the normal heart. This finding offers an explanation for the inability of the heart to tolerate any oxygen debt. Any increase in work by the heart must be met by an immediate increase in the available oxygen, which means an increase in coronary blood flow. Since there is no evidence that the resting heart has a reserve supply of closed capillaries which might open when the demand for more oxygen is sounded, it seems probable that the only method of increasing the supply is by an increase in the volume of blood flow through the capillaries already open.

During the past three years, in work with Drs. Gregg, Pritchard, and

Eckstein, an attempt has been made to compare the metabolism of normal and hypertrophied heart muscle with a simultaneous determination of the blood flow in those hearts. Thus far the method for the measurement of coronary blood flow in a chronic experiment has not proved satisfactory. A great deal of work on the stromuhr of Rein, which has been used so extensively by Essex, Baldes, Herrick, and others, has convinced us that the instrument is not a reliable one for the measurement of blood in coronary arteries in our experiments. It is our belief that many of the results in the literature obtained with the stromuhr are open to serious question.

The changes occurring in hypertrophy, therefore, increase the distance over which oxygen and metabolites must travel, and in the absence of any obvious compensatory mechanism, such as an increase in the myoglobin content, or an increase in the percentage saturation of O_2 in the coronary venous blood, one might raise the question as to whether hypertrophy is an actual hindrance to the efficiency of the heart. Whether a compensatory increase in the volume of blood flow in the coronary circuit occurs with hypertrophy is unknown.

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STUDIES IN VITAMIN A

Relation of Blood Level and Adaptation to Dim Light to Diet[1]

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What is meant by vitamin A deficiency? In the case of the rat the answer is comparatively simple since we are dealing with a unit deficiency under controlled conditions. In the case of the human the answer has varied. Twenty years ago the answer was simple—Xerophthalmia. Ten years ago deficiency could be recognized in the absence of corneal changes, but it was necessary to wait for the autopsy. At present the desire to obtain evidence of deficiency before anatomical changes have developed has led to the increasing use of two methods by which it is hoped to achieve this object: namely (1) the determination of ability to adapt to dim light, and (2) the measurement of the blue color obtained by the addition of antimony trichloride to a petroleum ether extract of serum. The purpose of the work reported here is to determine to what extent the use of these two methods is justified. It is not our purpose to review the controversial evidence regarding the use of measurements of adaptation to dim light, or to take part in the controversy; but merely to present what evidence we have and the conclusions we feel we can draw from it.

The plan of procedure was simple. Observations were carried out on those who visited the clinic for physical examination for placement in homes, because of tuberculosis contact, or at the request of various social agencies. The fact that these children were rarely suffering from any illness excluded factors that might have arisen from patho-

[1] The photoelectric colorimeter used in this work was obtained through a grant made by the Ella Sachs Plotz foundation.

logical processes capable of influencing the vitamin A level, and allowed us to concentrate our attention on dietary deficiency as it influenced the vitamin A and carotene of the blood and the ability to adapt to dim light. In each case when feasible a test of the adaptation was made and at the same time a sample of blood was taken for determination of vitamin A, carotene, and total lipids. In addition a general survey of the diet was made.

The measurements of light adaptation were made with the apparatus described at the end of the article. As a result of its use in the work reported here it is felt that this instrument or one devised on similar principles is more useful for the study of adaptation in children than the more elaborate instrument that depends on intelligent cooperation, to achieve the more accurate results of which it is capable. Its use is simple for the operator and so simple for the subject being examined that it was found possible to make measurements in children as young as 4 years of age. It is, of course, realized that shortening the time of the test renders it less delicate, so that minor grades of defect may not be recognized, but on the other hand fatigue and loss of interest are avoided, and for children these factors as well as that of education are important in limiting the usefulness of the more elaborate methods.

The vitamin and carotene were determined by a method derived from that of McCoord and Clausen, and similar also to that devised by May. The method was described in detail recently (1). In order to understand the terms used, it is necessary to point out that the blue color obtained when antimony trichloride is added to a petroleum ether extract of serum, is due to both vitamin A and carotene. Carotene is determined separately by measuring the intensity of the yellow color of the petroleum ether extract. The blue color is measured in "units," 1 unit corresponding to the amount of color produced by $\frac{1}{50,000}$ of a gram of a sample of haliver oil containing about 50,000 U.S.P. units per gram. In the tables and charts which follow, the term "total vitamin A" refers to the units represented by the blue color caused by both the vitamin A and the carotene of 1 cc. of serum. The term "vitamin A corrected" refers to the units represented by vitamin A after the units represented by carotene have been subtracted. The values for carotene have been given in gamma and it

was found that the blue color with antimony trichloride caused by 1 gamma of carotene corresponded to that caused by 0.4 unit of vitamin A. The term "carotene" refers to the mixture of Xanthophyll and carotene, no attempt having been made to separate the two.

The method for determining total lipids was described in the previous publication to which reference has been made.

The cases were divided into four groups. While adequacy of the diet was the primary consideration in the division, it was not found possible with the means at our disposal to determine as precisely as is desirable in a study of this nature exactly what the diet had been over a long period of time. To aid in the division, therefore, we have made use of certain subsidiary information such as the general intelligence of the parents, their financial status, evidences of care or neglect, *etc.*

Group I comprised the children from well-to-do homes, with excellent diets. Also included was a group of children from an orthopedic hospital school, and a few adults, nurses and students who volunteered for the test.

Group II included children from relatively poor homes but with evidence of good care and nutrition.

Group III included children whose parents were too poor to supply them regularly with the proper food, but whose condition indicated care and consideration for the child's welfare.

Group IV included those from the poorest homes with evidence of neglect. Included in this group is an adult with pellagra, as a result of alcoholism.

RESULTS

The results are contained in table 1. The figures have been further analyzed in a series of distribution curves (charts 1, 2 and 3). In these curves the effect that deficient diets have on the values obtained by the tests can be estimated by the amount of shifting as compared with curves representing optimal conditions (Group I). In the case of carotene the shift becomes progressively greater as one goes from Group I to Group IV. The shift in Group II is due principally to the fact that there are few figures above 1 gamma per cc. with concentration of the figures such that the median lies somewhat to the

TABLE 1

	GROUP I		GROUP II		GROUP III		GROUP IV	
	Number	Per cent of total	Number	Per cent of total	Number	Per cent of total	Number	Per cent of total
Carotene, gamma per cc. serum								
0 – .25	0	0	1	1.4	2	5	6	35
.25– .50	1	2.4	12	17	21	54	10	59
.50– .75	5	12	21	30	8	20.5	1	6
.75–1.0	12	29	23	32	6	15.5	0	0
1.0–1.25	11	27	11	16	2	5	0	0
1.25–1.5	5	12	3	4.2	0	0	0	0
1.5 –1.75	3	7	0	0	0	0	0	0
1.75–2.0	3	7	0	0	0	0	0	0
Above 2.0	1	2.4	0	0	0	0	0	0
Total cases	41		71		39		17	
Carotene, gamma per mg. total lipids								
0 –.025	0	0	1	1.8	0		5	29
.025–.05	0	0	1	1.8	5	15	5	29
.05 –.075	1	2.5	5	9	10	30	5	29
.075–.10	5	12.5	14	25	6	18	1	6
.10 –.125	12	30	13	23	3	9	1	6
.125–.15	5	12.5	9	16	2	6	0	0
.15 –.175	7	17.5	9	16	3	9	0	0
.175–.20	6	15	3	5.4	2	6	0	0
.20 –.25	2	5	1	1.8	2	6	0	0
Above .25	2	5	0	0	0	0	0	0
Total cases	40		56		33		17	
Vitamin A (total), units per cc. serum								
0 – .2	0	0	0	0	0	0	3	17.5
.2– .4	3	7	9	13	3	8	7	41
.4– .6	9	22	25	35	19	49	6	35
.6– .8	11	27	25	35	14	36	1	6
.8–1.0	9	22	8	11	2	5	0	0
1.0–1.2	5	12	2	2.8	1	2.6	0	0
1.2–1.4	2	5	2	2.8	0	0	0	0
1.4–1.6	1	2.5	0	0	0	0	0	0
Above 1.6	1	2.5	0	0	0	0	0	0
Total cases	41		71		39		17	

TABLE 1—*Concluded*

	GROUP I		GROUP II		GROUP III		GROUP IV	
	Number	Per cent of total	Number	Per cent of total	Number	Per cent of total	Number	Per cent of total
Vitamin A (corrected), units per mg. total lipids								
0 –.02	0	0	0	0	0	0	2	12
.02–.04	0	0	0	0	0	0	2	12
.04–.06	7	17.5	8	14	4	12	6	35
.06–.08	6	15	18	32	10	30	3	18
.08–.10	8	20	11	20	6	18	4	24
.10–.12	5	12.5	9	16	6	18	0	0
.12–.14	6	15	5	9	3	9	0	0
.14–.16	6	15	3	5.5	2	6	0	0
Above .16	2	5	2	3.5	2	6	0	0
Total cases	40		56		33		17	
Total lipids, mg. per cc. serum								
3–4	0	0	0	0	0	0	0	0
4–5	1	2.5	3	5.5	6	18	3	18
5–6	5	12.5	12	21	10	30	4	24
6–7	11	27.5	20	35	12	36	4	24
7–8	9	22.5	12	21	3	9	5	29
8–9	3	7.5	5	9	2	6	1	6
9–10	5	12.5	4	7	0	0	0	0
10–11	5	12.5	1	1.8	0	0	0	0
11–12	1	2.5	0	0	0	0	0	0
Above 12	0	0	0	0	0	0	0	0
Total cases	40		57		33		17	
Adaptation time, minutes								
0–2	3	15	8	14	4	13	1	6
2–4	7	35	22	40	11	35	1	6
4–6	6	30	21	38	14	45	2	12
6–8	3	15	3	5.5	2	6.5	3	18
8–10	1	5	1	1.8	0	0	4	24
10–12	0	0	0	0	0	0	3	18
12–14	0	0	0	0	0	0	1	6
14–16	0	0	0	0	0	0	2	12
Total cases	20		55		31		17	

Note: Considerations of space prohibit the presentation of the actual data from which this table is constructed. It seemed best to present the data in the form used in the construction of the distribution curves. It was thought that there were not enough cases to make a more detailed statistical analysis advisable, and it is doubtful if such an analysis would have given any clearer basis for understanding.

left of the median in Group I. In Groups III and IV the shift to the left is definite. In the case of the corrected vitamin A values on the other hand, the shift in Groups II and III is relatively slight compared with the shift in the case of carotene. It is only in Group IV that the shift becomes marked. This difference between the behavior of carotene and vitamin A is readily explained by the fact that caro-

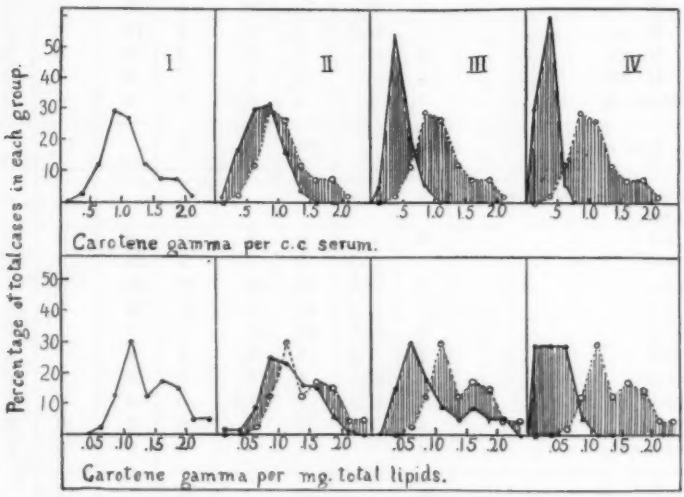

CHART 1. DISTRIBUTION CURVES FOR CAROTENE

Note: In this chart and the ones that follow, the curve of Group I (optimum conditions) has been repeated (as dotted lines connecting circles) in the frames in which the curves of the other groups are charted, in order to facilitate analysis. The shift is denoted by shading, leaving a clear space to denote the overlapping.

tene is not stored and is therefore more immediately dependent on the diet than is vitamin A, the deposits of which protect against a reduction of blood level, so that only when the conditions are at their worst is the vitamin A of the blood likely to be markedly reduced in the absence of pathological conditions.

In a recent publication it was pointed out that there was a roughly parallel relationship between the vitamin A and carotene, and the total lipids of the serum. As a result of this study it seems likely

that vitamin A and carotene exist in the blood in solution in the fat or at least closely associated with it, and that a reduction in the blood fat might be a factor in the reduction of vitamin A of the blood. Accordingly the ratio of vitamin A to total lipids has been calculated, and these ratios analyzed in the same manner as in the case of vitamin A levels of the serum. The differences between the two series of distribution curves are not very great but they probably have significance.

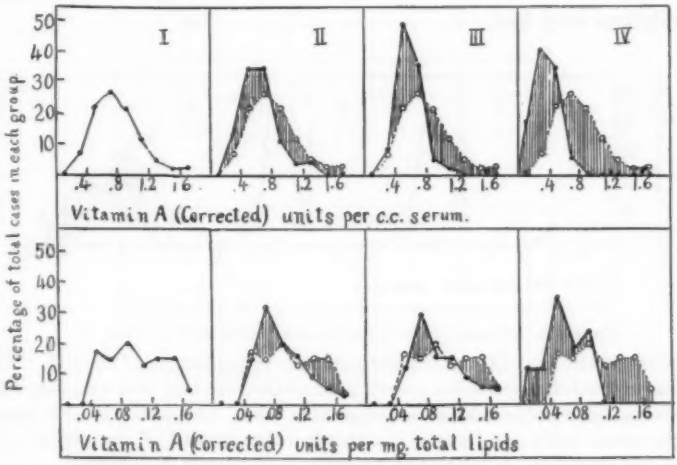

CHART 2. DISTRIBUTION CURVES FOR VITAMIN A (CORRECTED)

Note: The wide spread of the curve in the optimum group is disappointing to anyone who would like to be able to separate "normal" from "abnormal." While in Groups II and III lower values tend to predominate as compared with Group I, it is only in Group IV that there is any real shift in the curve.

As might be expected, since low vitamin A or carotene values are associated with low fat values, the curves tend to be extended toward the right and therefore have a somewhat broader base with less concentration of values at lower levels. In the second place the shift in the case of the corrected vitamin A in Groups II and III is insignificant. These two observations indicate that the blood fat may actually have an influence on the vitamin A level in these cases, and that possibly some of the low values for vitamin A in Group III may be

due to the fact that the lipid level is in general somewhat lower than in Group I or II, as may be seen in the table. In Group IV, on the other hand, the general lipid level is no lower than in Group III so that in this group, for the first time, one sees a shift in values due to the prolonged deficient diet. The conclusion reached from the first series of curves is therefore strengthened, namely: that the influence of deficient diet on the blood vitamin A level is largely confined to those cases in which the deficiency is most prolonged and the social conditions very bad.

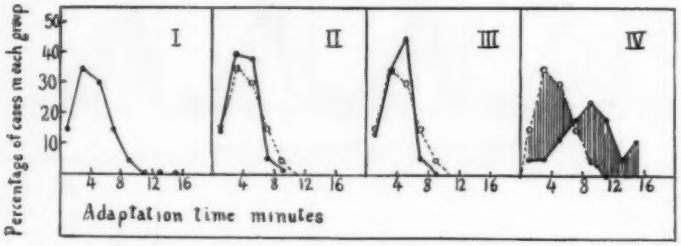

CHART 3. DISTRIBUTION CURVES FOR ADAPTATION TIME

Note: In this case there is virtually no shift in values except in Group IV. This means that only when the diet is very bad and has been bad for a long time, does it have an appreciable influence on adaptation time. The relatively wide spread of the curves in the first three groups should make one wary of interpreting relatively minor changes in adaptation as evidence of vitamin A deficiency.

In the case of adaptation time it is evident that there is a wide distribution of values in normal cases—from about two minutes to eight minutes, and it is a striking fact that the distribution in Groups II and III covers the same range and the form of the curves is virtually identical. Only in Group IV is there any shift.

In chart 4, adaptation time is plotted against the corrected vitamin A—both its concentration in the serum and in the serum lipids. Both halves of the chart show essentially the same thing: that there is some correlation but that the only clear results are that the vitamin A level of the serum over a wide range of values, has no appreciable influence on the adaptation time, and it is only at extremely low levels that the adaptation time is prolonged. From this it may be concluded that

while the vitamin A of the blood is undoubtedly a factor in the prolongation of the adaptation it is of decisive importance only when very low. Conversely the prolongation of the adaptation time can be considered as evidence of a low level of vitamin A only when it is marked.

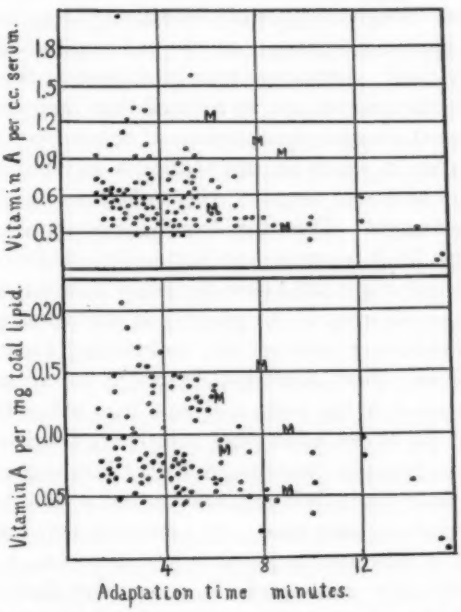

CHART 4. RELATION OF VITAMIN A OF SERUM TO ADAPTATION TIME

Note: While there is no very close correlation that could be expressed statistically, there does actually appear to be a relationship showing in the upper border of the area occupied by the points. It might be stated that the higher the values for blood vitamin A the less will be the probability that adaptation time will be prolonged. "M" refers to cases with myopia.

DISCUSSION

Judged by an anatomical standard we cannot say that any of these patients were deficient. If we are to be allowed to say that there was deficiency; we must find an answer to our original question: what

do we mean by vitamin A deficiency? In a certain group of cases we encountered (1) poor diets which, to judge by the child's condition, had extended over a considerable period of time, (2) blood vitamin A and carotene levels extremely low when compared with the usual, and (3) a marked prolongation of the adaptation time. It is altogether likely that we are justified in such cases in speaking of vitamin A deficiency even though evidence of anatomical change be lacking, for, after all, the anatomical changes are the end-result of deficiency, not the deficiency itself. Deficiency may be defined as the state that is reached when the reserves are so reduced that they are unable any longer to prevent changes characteristic of deficiency. Or it may be defined as a state in which the distribution is so interfered with that the tissues are no longer supplied with sufficient vitamin to prevent characteristic changes. These two definitions do not necessarily mean the same thing; for it is conceivable that under certain conditions the level in the blood might fall below the point at which adequate distribution is possible even in the presence of adequate reserves. Our conception of deficiency must actually include both these possibilities.

There is no way short of autopsy by which we can determine the stores of vitamin A in the body, and even then unless they are completely absent we do not know what constitutes deficiency. In rats, the stores have virtually disappeared a week before any visible signs of deficiency have made their appearance, and a week in the case of the rat is a relatively long time. An extraordinarily low level of vitamin storage is adequate to prevent deficiency; *i.e.*, it seems probable either that there is no gradually progressive diminution of distribution as the loss of stores progresses, or that the normal distribution is so much greater than necessary that it can suffer a large diminution without ill effects.

Since distribution occurs through the blood the importance of a knowledge of the level of vitamin A in the blood is obvious. But mere knowledge of the level of vitamin A is of no value unless we are able to learn its significance in relation (1) to storage and (2) to adequate distribution. It is well established that the blood level bears no constant relation to the stores, and the only conclusion we can reach is that a high blood level is inconsistent with deficiency. In the presence of a low blood level the question of deficiency, whether of stores

or distribution, is uncertain. The question whether there is a critical level in the blood below which there is likely to be deficiency can in the present state of our knowledge be based only on clinical experience. In the work reported here there appears to be a point below which the great majority of cases tended to have a prolongation of the adaptation time. This point lay at about 0.35 units per cc. (corrected vitamin A) on the scale used in this work.

It is therefore likely that a level of vitamin A (corrected) below 0.35 units per cc. serum is presumptive evidence of vitamin A deficiency especially in the presence of a defective diet or under conditions that might interfere with absorption from the gastro-intestinal tract. Figures above this point have little diagnostic value, at least at present, until we know more of the factors other than deficient reserves that might influence the blood level. Even below this point it would be well to be cautious in interpretation in the presence of pathological processes that might influence the blood level, such as acute infections, or catarrhal jaundice, or anything causing lowering of the total lipid level.

In the case of the adaptation time, there is a definite relation between a very much prolonged adaptation time, poor diet and low blood vitamin A. The results demonstrate once more the importance of vitamin A deficiency in prolonging the adaptation time. But just as in the case of the blood level, moderate prolongation has little diagnostic significance, and one cannot say that because marked prolongation is presumptive evidence of deficiency, moderate prolongation is evidence of a milder deficiency. There are evidently other factors that interfere with adaptation that cannot yet be evaluated. Myopia is one such factor as Hess has pointed out and as this work confirms.

In the cases studied here, therefore, the blood level has the same significance as the adaptation test in regard to its use in diagnosis, and the same limitations. In the case of each procedure we can obtain presumptive evidence of relatively severe deficiency in the absence of anatomical evidence; but we cannot yet by these means diagnose the mild deficiency or say in any given case that the vitamin A of the diet is insufficient for the child's needs unless it is grossly deficient.

SUMMARY

In a large number of children the vitamin A, carotene and total lipids of the serum as well as the adaptation to dim light have been studied in order to determine whether these values could be used to diagnose probable deficiency. The following conclusions can be reached:

1. The values obtained by the methods making use of Carr-Price reaction as described in recent publications, are compatible with the conclusion that this reaction accurately determines the vitamin A of the serum. This method has recently been attacked on theoretical grounds only.

2. A striking fact is the wide spread of values for vitamin A of the serum. Even in the optimum group values were obtained that were as low as the majority of values in the poorest dietary group. It is impossible therefore to say that a given vitamin A value is below the normal, though for diagnostic purposes one can give a figure below which values may be considered abnormally low. This figure lay at about 0.35 units (corrected) vitamin A per cc. serum on the scale used here.

3. While the carotene values were shifted downward with increasingly poor diet, the shift in vitamin A values was inconsiderable except in the poorest dietary group. In other words only in the presence of the worst conditions does the vitamin A of the serum give evidence of deficiency.

4. Likewise a shift in adaptation time was confined to the poorest group. As in the case of vitamin A the wide spread of values even in the optimum group, precludes the use of minor disturbances in the diagnosis of submaximal vitamin A deficiency.

5. A comparison of vitamin A of the serum and adaptation time establishes a general relationship that probably depends on the fact that both may be subject to similar influences. It does not support the hypothesis that adaptation time is necessarily influenced by the availability of vitamin A as represented by the level in the serum.

APPENDIX

The instrument used in this investigation was designed and made in collaboration with the technical expert of the Wilmer Institute. It operates on a principle

which is different from that of other instruments at present in use for measuring the adaptation to dim light, in that: (1) the end is not the seeing of a spot of light, but the recognition of certain details in a test picture illuminated by a dim light which itself is not seen; (2) this dim light is of a fixed intensity, comparison being made of the time required to recognize the details in the picture. Whereas in the usual method an attempt is made to measure the adaptation at a definite point in peripheral vision; in this method it is recognized that the attempt to measure adaptation at a fixed point on the retina is likely to fail in children, and a method is used that admittedly is probably not as delicate in its results. Not only has the principle of a fixed point on the retina been abandoned, but the light intensity is such that a person with normal adaptation should average about four minutes or less.

For these reasons the results recorded here can have no part in the current controversy regarding the use of the measurements of adaptation to dim light in recognizing minor grades of vitamin A "deficiency" or in determining the optimum dose of vitamin A. The results, however, do indicate the usefulness of this method of measurement in the recognition of what might be called a "dangerous" depletion of the vitamin A reserves.

The details of the instrument and a comparison of the results with those obtained from an instrument of the Hecht type will be published separately when the investigations are completed. A few statements regarding the procedure may be made here. A preexposure to bright light for three minutes is made during which the child looks into the box at a few line drawings on a white background illuminated by two 150 watt lamps. At the end of this period the bright lights are switched off, the dim light switched on, and the preliminary pictures replaced by the test picture. The yellowish color of the dim light is corrected by a blue filter and its intensity is kept constant by frequent photometer measurements and regulated by a rheostat set in the circuit supplied by two dry batteries. It is sometimes desirable when the child is becoming fatigued, especially when the adaptation time is prolonged, to raise the illumination to a point where the picture can just be seen, then to lower the illumination to its previous level. After all there is no reason to expect a child to continue to stare indefinitely into a black hole in which there is nothing to be seen. A little added interest improves cooperation.

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A RESULT OF CONTACT WITH A 2400 VOLT CIRCUIT

Report of an Unusual Case

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Numerous studies have been made of the structural and functional alterations which occur in living tissue brought into contact with various electric circuits. Jaffé (1928) has published a thoroughly comprehensive review of the subject titled *Electropathology*. Langworthy and Kouwenhoven (1932) described types of electrical injuries involving different organ systems, incorporating many observations of their own with a survey of the literature. These authors have compiled other authoritative reports of similar nature derived from clinical and experimental sources. Recently a series of eighteen cases of electric burn was presented by Edwards and Bowie (1940). Their discussion covered a wide variety of types of injury and reflected excellent skill in treatment.

Consideration of the recorded experiences of others soon reveals that the kinds of injury following contact with electric circuits are legion. The results may be immediate or delayed or both, and range from a simple local burn of the skin to deep charring and widespread necrosis involving any tissue. Due to progression of blood vessel or nerve impairment, late disorders of structure and function occasionally develop at a distance from the original injury. The character of the primary damage is determined by certain specific factors. These include (a) the type of current (alternating, direct or surge), (b) voltage, (c) amperage, (d) path through the body, (e) resistance of the body in the path of the current, (f) character of contact and conductors and (g) duration of the contact. The individual details of cause, effect and outcome in relation to these variables have been adequately treated elsewhere. It is the purpose of this paper to present and discuss a case of an unusual type of injury which resulted from accidental contact with a 2400 volt circuit.

CASE REPORT

G. J. A. (J. H. H. 190,106), a 29-year-old white farmer, was admitted to the Johns Hopkins Hospital on December 17, 1939 complaining of weakness and pain in the left shoulder, arm and hand following an "electric shock."

The patient had been injured September 1, 1939 while working on his farm near Westminster, Maryland. One of the four wires of a three phase, 4000 volt, 60 cycle power transmission line in the vicinity had broken and fallen across an electric fence surrounding a pasture. The potential between this cable and the ground was 2400 volts. A quarter of a mile away, the patient was opening a wooden gate connected with the overcharged fence when the circuit contacted his left arm or hand and grounded through his body. He was knocked down instantly and rendered unconscious for several minutes. Upon recovery, he was weak and dazed but soon noticed that his entire left arm was practically powerless from the shoulder.

Since the patient was alone when the accident took place, no exact details were available for an analysis of the factors concerned. There were several points of immediate interest, however. It was considered likely that the patient had not actually touched the conductor, although the manner and location of the contact remained in doubt because there were no current markings or burns of any sort on the skin. Furthermore, the amperage to which the victim was subjected could not be estimated because the resistance offered by the circuit and ground path was problematical. The potential was sufficient, nevertheless, to cause a generalized muscular contraction which hurled the patient's body eight or ten feet from the site of contact. The resistance in the circuit through the body from conductor to ground was probably very high since the weather was clear and the ground dry. It was not known whether contact was made with the skin directly or through clothing, although Mr. A. was sleeveless at the time. The duration of the contact was, of course, momentary.

Following injury, the patient's arm remained weak and in a few days had become swollen, hot, tender and extremely painful on motion. Large bruised areas appeared in the skin spontaneously and subsided slowly. After several weeks the arm began to shrink in girth and "draw up." Some degree of swelling persisted in the forearm. Paresis, pain and tenderness continued, and numbness was noticed in the hand. Bruises and new deep painful swellings recurred without apparent cause. Periods of generalized systemic reaction were evident, probably due to toxic resorption from the damaged tissues. The patient lost appetite and weight, suffered headaches and had spells of nausea and vomiting. Because of the great discomfort, he was forced to remain quiet most of the time and was quite unable to do work of any sort. He was attended by his own physician for several months. Finally, as the condition of his arm remained essentially unchanged and presented such a unique picture, he was brought to the hospital for further study and treatment.

The patient's family record and past history were non-contributory. He had enjoyed excellent health before his accident.

Except for the injured left arm, the physical examination during hospitalization disclosed nothing significant. Temperature, pulse and respiration were normal.

The blood pressure was 120 systolic and 80 diastolic. Routine laboratory studies, including urinalysis and a serological test for syphilis were negative.

The damaged arm was held close to the body and showed changes suggesting an early muscular atrophy with contracture. The elbow was bent at 90 degrees and the fingers and wrist were kept in a moderately flexed position. This posture resulted in part from paralysis, atrophy and contracture, otherwise from an endeavor to minimize pain. In fact, any attempt at active or passive movement would precipitate such severe discomfort in the muscles and joints involved that the arm could be handled only with the greatest care. A sling or the opposite arm was always used to provide suitable support.

The skin of the arm seemed of normal texture and exhibited no scars. The hair was undisturbed. The posterior surface of the upper arm was mottled by an old bruise. Over the dorsum of the forearm was a firm diffuse swelling, red, warm and extremely tender, apparently originating in the deep tissues. The dorsum of the hand was edematous but not discolored or tender. The skin of the left palm was cold and moist in comparison with the right. There was no indication of infection at any point and no enlargement of the epitrochlear or axillary lymph nodes.

The left upper arm was 3 to 4 centimeters smaller in circumference than the right, including some reduction in prominence of the deltoid. The left biceps and triceps were flabby and diminished in size. The left forearm equalled the right in girth because of the swelling which obscured the condition of the underlying muscles. There was slight atrophy of the left thenar and hypothenar eminences. The left shoulder sagged a little but the musculature was not visibly altered. No joint damage was evident.

Power was reduced or absent in the affected muscles, although strength could not be estimated readily because of pain. For this reason, voluntary movement in the shoulder was restricted to slight abduction and internal rotation. Feeble and limited motion was possible at the elbow. The fingers and wrist could be flexed a little but extension of the wrist was barely perceptible. The fingers could not be extended at all. Abduction and adduction of the fingers and opposition of the thumb were minimal. No muscular fasciculations could be detected anywhere.

Definite sensory changes were demonstrable as a cutaneous "glove" hypesthesia extending almost to the elbow and involving all modalities. This condition merged into normal skin sensitivity at the shoulder with no sharp sensory demarcation. Except for the conspicuous hypersensitivity to deep pain, deep sensibility was diminished when tested by vibration and passive movement. The biceps, triceps and supinator jerks, of normal intensity on the right, could not be elicited on the left.

The patient was examined by specialists who had had previous experience with electrical injuries. All agreed that his case was most unusual in that extensive damage had been inflicted on the deep tissues of the arm without affecting the skin.

In order to help form some opinion of prognosis, it was determined to do an exploratory operation. Accordingly, a small incision was made under gas anesthesia over the firm swelling on the dorsum of the left forearm. The subcutaneous tissue appeared normal. Beneath the deep fascia, however, there was evidence of old

hemorrhage with numerous clots. The underlying extensor muscle was described by the operator (Dr. George E. Bennett) as having the appearance of "cooked meat." A small piece of muscle, fascia and subcutaneous tissue was removed for microscopic examination. Although the tissues were somewhat friable, little bleeding developed and the wound was closed with several black silk sutures. The edges of the incision held together for several days after removal of the stitches, but coaptation was poor. The wound finally broke open and released a persistent sero-sanguinous discharge. For the next ten months the wound failed to heal in spite of various types of treatment; only sluggish easily-bleeding granulations were formed.

Microscopic examination of the biopsy specimen (figures 1 to 4) revealed extreme tissue alterations. In the subcutis as well as in the deeper structures there were large necrotic and hemorrhagic areas infiltrated with phagocytes and young fibroblasts. The adipose tissue had lost its normal appearance and in many places seemed to have undergone liquefaction. In the region of functioning blood vessels, organization was progressing in typical fashion with proliferation of connective tissue cells and new capillaries. Elsewhere, particularly in areas containing damaged and thrombosed vessels, there was evidence of old and new hemorrhage with little or no attempt at organization. No normal-looking striated muscle could be found. In its place were large hemorrhagic and necrotic masses occasionally traversed by groups of damaged muscle fibers. These stained evenly and bore evidence of coagulation with hyalinization, swelling and shrinkage, loss of cross striations, pyknotic or absent sarcolemmal nuclei, and separation and fragmentation of individual fibers. Vascular abnormalities were conspicuous. Most of the larger vessels showed a cellular reaction in the adventitia, thickening of the vessel wall and old and new thrombi in the lumen. There was occasional recanalization and considerable new blood vessel formation. Many of the smaller vessels were empty or also contained thrombi. Some were surrounded by mononuclear collars and exhibited damaged walls.

The patient's course in the hospital was uneventful. He was discharged December 22, 1939. Treatment was restricted to general supportive measures with complete rest and sterile dressings for the injured arm. Further observations were made during subsequent monthly visits.

Roentgenograms of the left shoulder, arm and hand taken November 4 and 28, 1939 were negative. However, a film (figure 9) made on January 27, 1940 disclosed an opaque mass adjoining the middle of the radius which was interpreted as calcium deposition in an old subperiosteal hemorrhage. At a later examination on October 27, 1940, little change was noted. There was slight rarefaction of the long bones due to disuse but no evidence of joint damage and none of the delayed osseous changes known to develop occasionally after electrical injuries.

The patient was reexamined March 20, 1940, three months after operation and six and a half months after injury. At this time photographs (figures 5 to 7) were made of the injured arm. All evidence pointed to slowly progressive tissue involution with muscular atrophy and little or no attempt at repair. The changes still followed the pattern of damage noted earlier during hospitalization. The biopsy wound remained

open, drained slightly and exhibited delicate granulations. There was some thickening of the skin borders but no sign of recent epithelialization. The atrophy of the forearm muscles had become more marked than that in the upper arm. Restricted feeble voluntary movement was possible, still limited by pain and contracture. A tender swelling had developed at the insertion of the deltoid, with slight skin discoloration. The sensory and reflex abnormalities were unchanged. In general, the patient had adjusted well to his handicap but was still unable to work.

Six months later, on September 10, 1940, there was remarkably little change in the condition of the arm. An extremely tender hematoma had developed spontaneously above the elbow. Considerable pain and tingling persisted in the forearm where the operative wound remained as before. Slight movements of flexion and extension were still possible in wrist and elbow together with feeble flexion of the fingers. There was no progression in the contractures and no joint changes or edema. Atrophy of the thenar, hypothenar and interosseous muscles had advanced. The shoulder muscles remained normal. The skin of the hand was now anesthetic, and more marked hypesthesia extended to the shoulder. Impairment in position and vibratory sense had also progressed. The left palm was cold, sweaty and mottled in contrast to the right and the skin of the fingers had become smooth and shiny. The patient's appetite remained poor and attacks of nausea and vomiting had recurred during the previous several months.

By October 1, 1940 the biopsy wound had begun to heal but the clinical picture otherwise remained static. On November 20, 1940 the wound on the forearm was covered with a thin vascular scar (figure 8) but several new painful swellings and bruised areas had appeared on the upper arm near the elbow. There was no evidence of any improvement in function.

The patient was readmitted to the hospital February 16, 1941 because of increasing pain in the injured forearm and more frequent headaches, nausea and vomiting. His symptoms seemed to have become more marked after the operative wound healed. He was quite weak and exhausted. Objectively, the condition of the arm had changed little. Contracture of the finger flexors had advanced slightly, suggesting Volkmann's ischemic deformity. Subcutaneous and deep hemorrhages had continued to recur and undoubtedly interfered with the progress of tissue repair and rate of muscular contracture. In the hope of relieving pain due to abnormal internal pressure, three longitudinal incisions were made into the deep tissues of the left forearm. As before, dark sero-sanguinous fluid exuded from the wounds. The fascial layers were bound together and thickened to the consistency of heavy leather. Trabeculae of scar tissue extended into the deeper structures and formed constraining loculi for the necrotic and hemorrhagic material. Relief was prompt as soon as drainage was well established.

Microscopic examination of muscular tissue removed at this time disclosed a remarkable advance in the process of organization. The old hemorrhages had been replaced by scar tissue which extended between groups of necrotic muscle fibers adjoining apparently healthy ones. For this reason, the material had a peculiar patchy appearance. The necrotic areas (figure 11) were characterized by hyalinized and

vacuolated muscle fibres, a chronic inflammatory reaction, scarring, and the remains of collapsed blood vessels which suggested an underlying circulatory disturbance. Elsewhere (figure 10), muscle fibers and blood vessels were normal-looking. Of particular significance was the absence of muscle regeneration in the damaged areas. The picture in general represented a poor attempt at structural restitution.

DISCUSSION

The changes which occur in living tissue during or immediately after the passage of an electric current are produced by heat, electrolysis and mechanical trauma according to the variables stated. Heat is generated in relation to the strength of the current and the resistance of the circuit. Death of tissue is accompanied by liquefaction of fat and coagulation of protein, especially that of blood, muscle and connective tissue. In extreme cases, carbonization of organic matter, vaporization of water, and fusion of bone take place. Electrolytic activity, most marked with direct current, contributes to cell death or may change the cellular organization of any tissue in such a way that growth and metabolism are temporarily or permanently altered. The conductivity of nerve trunks is usually impaired in this regard, motor activity failing before sensory. Extensive mechanical damage can result from the severe generalized muscular contraction caused by the electric current. Spasm may be restricted, however, to the extremity through which the current enters. Muscles may rupture, tear away from their connections, cause luxation of joints or even fracture the bone to which they are attached. If steam is generated, its expanding force may add to the damage in deep tissues or in confined spaces such as the medullary cavity of long bones or the cranial vault.

The late manifestations of electrical injury are determined by the type and extent of the immediate damage. Most conspicuous, perhaps, are those due to vascular disturbances. Progressive thrombosis in the injured vessels may overwhelm both the main and collateral blood supply and lead to extensive infarction. The remaining vessels, together with any new vessels, are obliged to carry their usual burden with weakened, friable and permeable walls. Consequently, they are liable to rupture either spontaneously or after minor trauma and continue to produce large superficial or deep hemorrhages. Edema may appear as a result of venous or lymphatic obstruction. Death of tissue frequently extends beyond the original necrosis, due probably to an inability of the weakened

cells to withstand the combined effects of impaired circulation and increasing local toxicity. For the same reason, repair is sluggish and inadequate, and in some instances the tissues appear to have undergone a certain intrinsic and permanent functional alteration. According to Langworthy and Kouwenhoven (1932), "it seems as if the defense reactions of the tissues had been paralyzed. . . .the altered tissue breaks down slowly, presenting the picture of an aseptic necrosis without pus formation." The devitalized material eventually arouses some local foreign body response and may cause generalized systemic intoxication. Stubborn infections, of course, are likely to develop in open wounds. Late neuropathic phenomena sometimes appear in association with the circulatory changes at the site of injury. Progression of damage in peripheral nerve trunks or delayed alterations in the central nervous system may lead to paralytic manifestations, sensory disturbances or vasomotor and neurotropic abnormalities. These, in turn, will also affect tissue growth and repair.

The characteristics of lesions produced in different organs by electric currents were discussed at length by Jaffé (1928). A few remarks concerning the alterations which are known to occur in blood vessels, muscles and nerves may be of interest here.

The progressive character of wounds caused by electricity seems due primarily to extensive alterations in blood vessels. The wall of the vessel through which a current has passed is brittle and friable. In small vessels, the endothelium is damaged and parietal thrombi are attached to the intima. According to Pearl (1933), the muscle fibres of the larger vessels are profoundly affected while the cooling effect of the circulating blood protects the intima. Arteries are sometimes so friable that ligation is impossible. Experiments performed by Jaffé *et al.* (1929) indicated that these changes are due to heat and not to some specific effect of the current. Martin *et al.* (1924) examined the arteries of an extremity 8 days after it had been severely burned by an alternating current at 10,000 volts. They observed separation of the elastica interna from the media, necrosis of media and, to a lesser degree, of intima, poor defense reaction and no thrombosis. The authors noted that a similar picture followed exposure to radium.

The changes produced in voluntary muscle are the direct result of

tissue burning or are brought about by damage to blood vessels and motor nerves. Ischemic contracture and paralysis are frequent end stages. Macroscopically, the muscles are said to be firm, dry and friable with changes extending far beyond the lesions on the surface of the body. Balkhausen and Grueter (1923) emphasized the relation of the muscle damage to the state of contraction or dilatation and engorgement of the blood vessels. They described a displacement of the contractile elements; instead of the usual fine cross striations, coarse hyaline transverse bands were seen microscopically, giving the impression that the entire sarcolemma of each fibre was separated into groups. This condition of the contraction bands ran parallel to the emptiness of the blood vessels, so that the muscle examined soon after injury resembled "white fish meat" wherever the vessels were collapsed and bloodless. Schmidt (1910) first observed this phenomenon. He demonstrated with the high power lens that there was no interruption in the continuity of the muscle fibrils which passed intact through the hyaline "bands." He considered the bands simply as compressed anisotropic discs. Noteworthy in this regard is the work of Carey (1940) who studied the microscopic structure of striated muscle in heat rigor in the course of his investigations of the wave mechanics of muscle. He showed that heat rigor of short duration is microscopically characterized by nodes and internodes and that the pressure nodes of the striated fibre contraction have deep differential chemical staining. Homogeneous nodes form in intense heat rigor and resemble those of Zenker's degeneration accompanying the high temperature and severe intoxication of typhoid fever and pneumonia.

In his treatise on industrial accidents caused by electricity, Panse (1930) has discussed the various aspects of injury to the nervous system. Peripheral nerves may lose their irritability and conductivity following electrical contacts. Urquhart and Noble (1929) showed experimentally that a block develops in nerve trunks if they are traversed by high tension currents. After a certain period, depending on the severity of the structural damage, conductivity returns. Bolognesi (1915) produced swelling and twisting of axones with breaking down of myelin sheaths in rabbits. Severely damaged nerves become friable and yellowish gray, never to regain function. However, unless changes have occurred in

the central nervous system, the function of injured peripheral nerves usually tends to improve with time.

An analysis of the factors available for consideration in the present case throws little light on the remarkable end result. It is certain that a powerful alternating current flowed momentarily through the patient's arm. The contact created no immediate localized skin lesion but produced widespread and enduring nerve, muscle, blood vessel and subcutaneous tissue damage limited to the injured arm.

Alterations in the subcutis included liquefaction of fat, thrombosis of small vessels and hemorrhage. The muscles themselves showed evidence of extensive tissue death and coagulation which presented a "cooked meat" appearance. No typical transverse hyaline bands were seen microscopically, probably because the changes were of long standing. Blood clotted in the larger vascular channels and damage to vessel walls promoted further thrombosis. Conductivity was probably impaired temporarily in the deep and superficial nerve tunks. There was no bone or joint destruction.

Subsequently, vascular changes progressed to impair circulation in the deep tissues. Continued thrombosis and a hemorrhagic diathesis due to fragility of vessel walls led to foci of ischemic necrosis as well as deep and superficial hemorrhages. The extent of the vascular damage was outlined by the numerous bruises which appeared widely over the injured arm. Late intermingled with earlier alterations to produce a bizarre picture at the time of the first biopsy. The large amount of dead tissue and clotted blood set up a considerable local foreign body response and, from time to time, precipitated generalized systemic reactions marked by headaches, nausea and vomiting. These symptoms were less severe after the necrotic material was released by incision. Circulatory disturbances were probably responsible for faulty nutrition in nerve trunks and a progression of anesthesia. This seemed paradoxical because impaired function caused immediately by electrical injury of nerve fibres usually tends to improve. Deep pain sensibility was probably maintained in part by the damaged nerve trunks but also could have been mediated through periarterial sympathetic afferents carrying stimuli from the thrombosed vessels. The true extent of interference with motor nerve activity was masked, of course, by the severe damage to the muscles

themselves. The usual bone changes concomitant with disuse were evident.

In accidental electrical injuries the contacts are usually poor. The electrodes may touch only a small area of skin or, in high tension accidents where the contact is often imperfect, a layer of air is interposed between skin and conductor. This layer is crossed by an arc formation in which some of the electromotive force of the current is spent. As a rule, if the resistance at the points of contact is low, general effects are severe and skin burns slight; if the resistance is high, superficial burns are severe and general effects slight. Likewise, most damage occurs wherever the tissue resistance is high in the path of the circuit. Hence, in cases where contact with the circuit has been made with the hand, the most severe changes may develop in the region of the elbow where there is little soft tissue.

In our case, it is conceivable that the skin resistance could have been so low and the contact so large and brief that the charring effect of a high resistance contact over a small area was avoided. Once penetrated, the skin acted as a confining insulator for the current which flowed in a low resistance path through the deep tissues, particularly the vascular bed and the muscles. It was in this narrow tissue conduit that the preponderance of damage occurred. Having reached the body-arm juncture, the current diffused through the trunk and failed to do further injury. Furthermore, no damage took place in the legs and feet where ground contact was made.

At present, the ultimate prognosis in our case is still in question. Damage to certain deep tissues is apparently extensive, progressive and intractable. The final healing of the first operative wound was encouraging. However, the normal processes of repair in the injured arm seem to be limited by hemorrhage and an inadequate circulation resulting from some permanent alteration in the blood vessels themselves. The lapse of almost one and a half years has brought little practical improvement in the use of the arm. Examination of the tissues at the end of this period showed normal scarring and other changes representing a genuine attempt at repair. Nevertheless, definite abnormalities in blood vessels, a chronic inflammatory reaction with foci of necrosis and lack of muscle regeneration were still conspicuous and are undoubtedly responsible for the persistent functional impairment. Considering the

symptoms and signs together with the structural evidence, therefore, it is generally accepted that little hope for an eventual satisfactory return of function can be entertained.

Treatment has been restricted to supportive and mild physiotherapeutic measures. Great care has been taken, of course, to prevent further injury of the weakened tissues. Large amounts of vitamins B_1 and C have been recommended. Pavex was considered as a possible method of encouraging vascular reorganization but would only be likely to accentuate the hemorrhagic tendency. Likewise, stellate ganglionectomy or cervical sympathetic ramisection could be performed as a means of obtaining relief from pain as well as encouraging tissue repair by permitting prolonged vasodilatation in the affected arm. However, an alteration of this sort might also increase the existing vascular embarrassment by promoting a greater number of hemorrhages. Finally, operative removal of the useless and painful extremity would be indicated if any aggravation of its present condition took place. This would be certain to entail considerable risk because of the friable condition of the blood vessels and the sluggishness of tissue repair.

SUMMARY

A case of an unusual type of injury following contact with a 2400 volt circuit is described. An attempt is made to analyze the structural and functional changes, both immediate and delayed, which resulted from the passage of the current in this case. Prognosis and treatment are discussed. The factors concerned in tissue damage, due to electricity, are reviewed.

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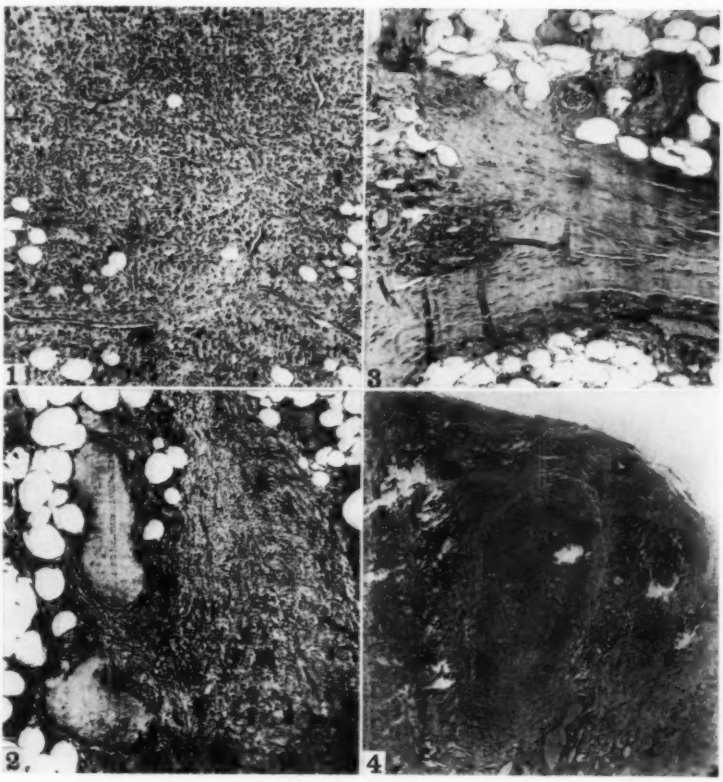
PLATE I

FIG. 1. Photomicrograph (72 diameters) showing the appearance of the subcutaneous tissue removed through the extensor surface of the left forearm three and a half months after injury. The damaged connective and adipose tissue has been infiltrated with phagocytes and young fibroblasts. Revascularization is following the advancing fibroblastic activity in characteristic fashion.

FIG. 2. Photomicrograph (100 diameters) demonstrating subcutaneous hemorrhage and impaired blood flow. The vessels contain hyalinized red cells. In contrast to Figure 1, organization here is retarded by the vascular damage.

FIG. 3. Photomicrograph (72 diameters) of a group of coagulated and hyalinized muscle fibers. The fibers stain homogeneously and show no transverse hyaline bands. There is swelling and shrinkage, loss of cross striations, pyknotic or absent sarcolemmal nuclei and separation and fragmentation of individual fibers. Some adjacent blood vessels are thrombosed.

FIG. 4. Photomicrograph (33 diameters) of a larger blood vessel filled with a partly organized thrombus. Some thickening of the vessel wall and a cellular reaction in the adventitia has occurred. A moderate cell response in the surrounding necrotic and hemorrhagic material is also present, especially in the vicinity of smaller vessels. Organization is poor.



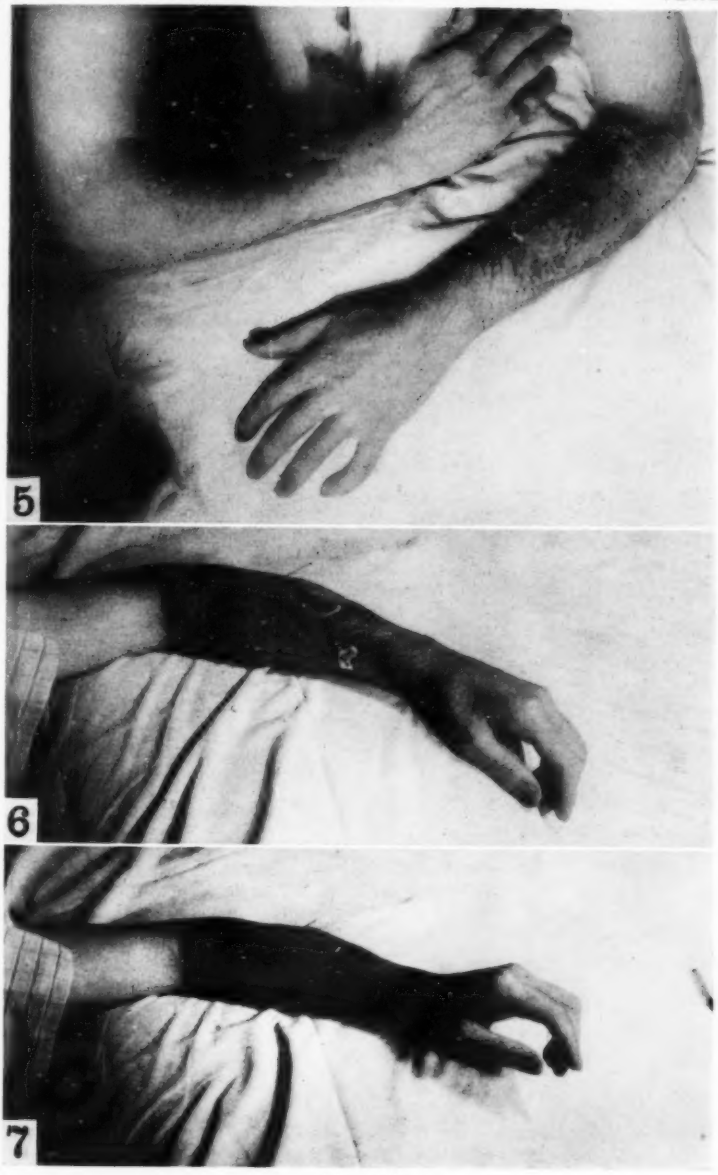
FIGS. 1-4

PLATE II

FIG. 5. The condition of the injured arm six and a half months after injury and three months after operation. The atrophic changes in the forearm and the indolent operative wound with raised edges and granulating base are visible. The arm and hand are held in their customary position.

FIG. 6. The arm in optimal resting position with flexion of elbow and slight flexion of wrist and fingers.

FIG. 7. The limit of extension in the wrist (compare with Figure 6). The fingers do not change position, although the patient is trying to extend them.

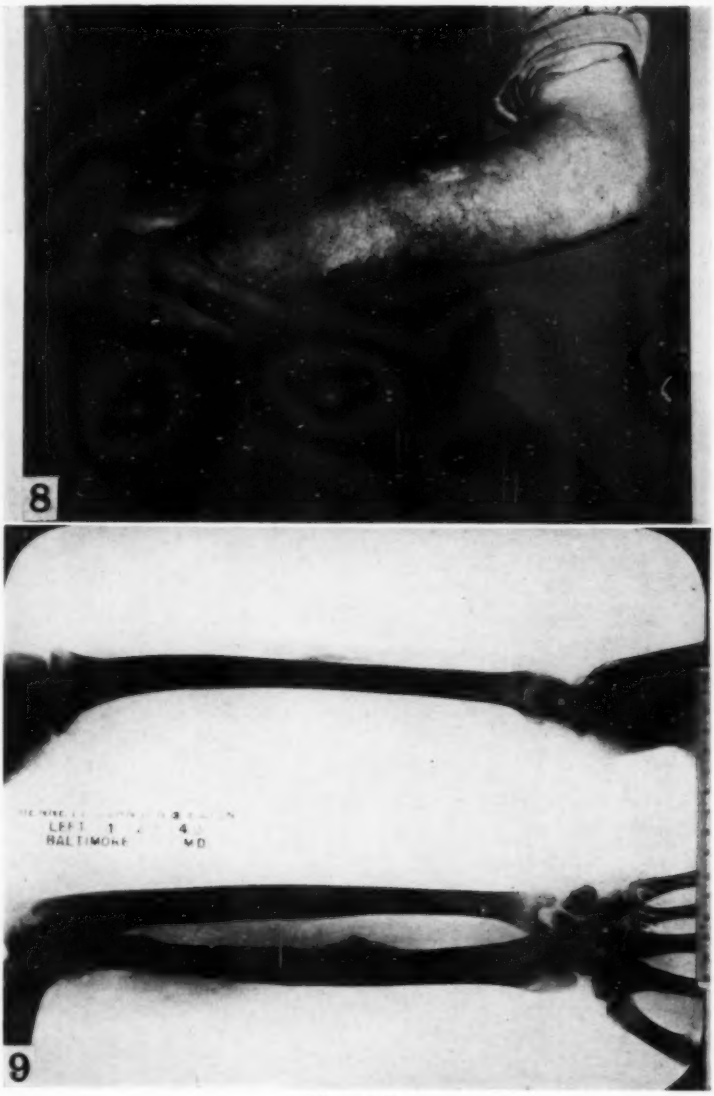


FIGS. 5–7

PLATE III

FIG. 8. The condition of the injured arm after fifteen months. The arm is supported in its usual position. A scab and thin vascular scar have finally covered the operative wound.

FIG. 9. A roentgenogram of the left arm made five months after injury. Adjoining the middle of the radius is seen an opaque mass produced by calcium deposition in an old subperiosteal hemorrhage. The rarefaction of disuse has not yet become evident.

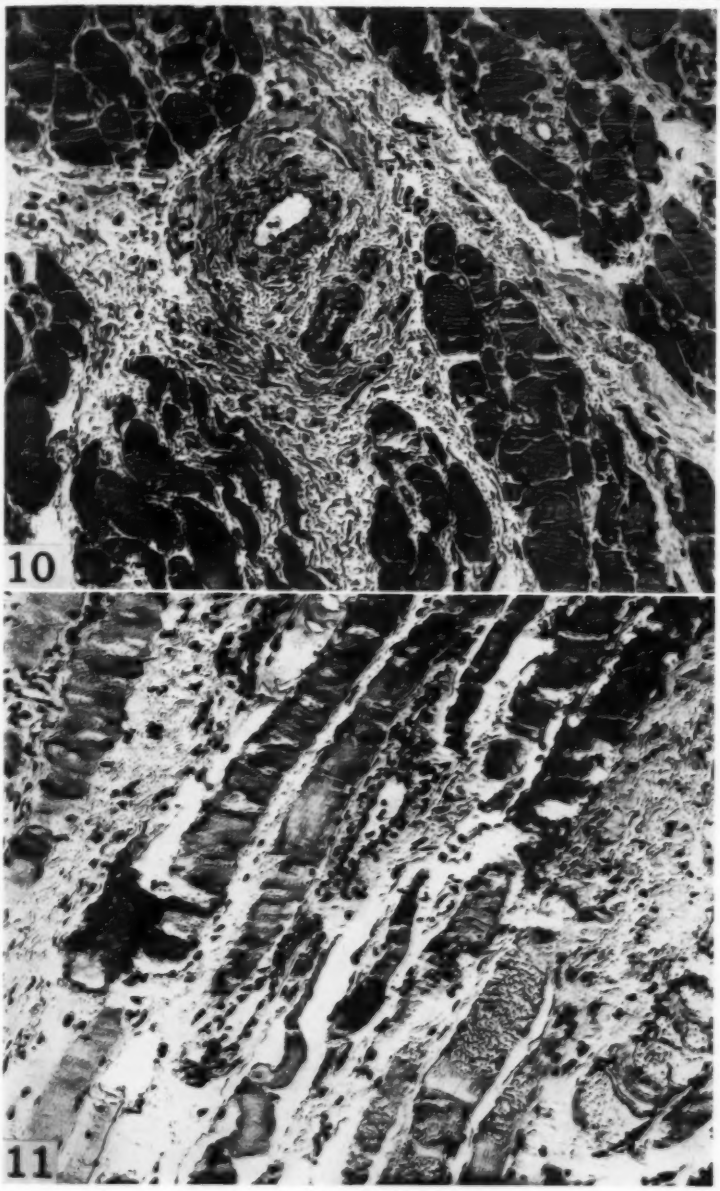


FIGS. 8–9

PLATE IV

FIG. 10. Photomicrograph (180 diameters) of tissue removed from the left forearm one and a half years after injury. The muscle fibers and blood vessels in this region are essentially normal in appearance.

FIG. 11. Photomicrograph (180 diameters) of an area adjacent to that shown in Figure 10. Hyalinized and fragmented muscle fibers in various stages of disintegration, a mild chronic inflammatory reaction and considerable scar tissue are present. Some of the fibers retain cross striations and suggest recent degeneration. There is no attempt at muscle regeneration. A collapsed blood vessel is visible in the center of the field.



FIGS. 10–11

UNIV. OF MICH.

MULTIPLE SELF-INFLICTED SUBCUTANEOUS ABSCESSES

Case Report

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From the Department of Medicine of The Johns Hopkins Hospital

Submitted for publication March 19, 1941

From time to time, the more interesting cases of self-inflicted skin lesions are reported in the literature. Stokes and Garner (1) present a good discussion of diagnosis and give a classification. Thomas (2) presents a brief analysis of the patient with "dermatitis artefacta." There are many case reports, but one by Delmas-Marsalet, *et al.* (3) resembles most closely the present case.

The patient was a forty-six year old married female store manager who entered the Johns Hopkins Hospital on December 5, 1940, complaining of recurrent subcutaneous abscesses of two years duration. Her past history and family history are non-contributory.

On admission the patient gave the following story: In May, 1938 she was bitten on the left hand by a black widow spider. There soon developed local swelling, cramps in the limbs and abdomen, chills and fever, vomiting, and coma; recovery ensued. During the Summer of 1938, she suffered recurrent chills and fever in attacks occurring every two weeks, associated with vomiting and back pain radiating into the legs. She was informed that she had pus in the urine, and was cystoscoped. In August 1938, after examination in a large clinic, she was told that she had "pus in the blood, abscess of the right kidney, and pus coming from both kidneys." Three months later, two subcutaneous abscesses appeared on the dorsum of the left hand and six on her abdomen; these were indurated, red, and painful. Concomitantly she suffered a severe attack of chills and fever. Five days after onset, the abscesses were drained surgically, and staphylococci and streptococci were cultured from the pus. In the two succeeding years she had repeated attacks characterized by prodromal arthralgia, followed by chills and fever, back pain, and sometimes collapse and coma. On the second day of each attack subcutaneous abscesses rapidly appeared everywhere on the body. The chills continued for a few days. Between the fifth and eighth days the abscesses were always drained under ether anesthesia. The interval between attacks varied from four days to four weeks. Chills and fever never occurred without the subsequent appearance of abscesses. During these two years there was a weight loss of fifty

pounds, progressive dyspnea, anginal attacks, chronic cyanosis, and severe nausea and vomiting. With each attack, she entered a local hospital for drainage of the abscesses, daily parenteral fluids, and blood transfusions. In addition she received at different times liver extract, sulfanilamide, sulfapyridine, autogenous vaccine, staphylococcus toxin, and supportive therapy. The last attack, which occurred four weeks before admission, was her most severe one; after partial recovery she was referred to us by her physician.

On admission the temperature, pulse, and respirations were normal; blood pressure 110/64. She was emaciated, dehydrated, extremely cyanotic, and there was an odor of acetone on the breath. She displayed unusual indifference toward her illness; elaborated her story in great detail; and seemed to be enjoying herself. There was moderate tenderness over most of the bones. The examination of the head, heart, and lungs was negative. Both the liver and spleen were palpably enlarged, firm, and tender. Pelvic examination revealed chronic cervicitis. The neurological examination was negative. Distributed over the skin of the abdomen and lower back, the left buttock, forearms, and thighs were innumerable scars of healed subcutaneous abscesses. There were also a few scattered over the shoulders, left side of neck, and scalp; none on the face, chest, or upper back. Several of the lesions were still red, indurated, and slightly tender. The hemoglobin was 80 per cent or 14.5 grams; the leukocyte count was 7700, with a normal differential count. The sedimentation rate was 2 mm., corrected. Serologic tests for syphilis were negative. The urine showed acetone and diacetic acid, but no other abnormality.

On the day after admission, suspicion was aroused by the distribution of the lesions, their appearance, and the attitude of the patient. Although she denied the possession of any medicines, examination of her belongings revealed the presence of a bottle of large white tablets, a syringe and hypodermic needle, and a rubber-stoppered ampule of purulent looking material. Culture of the latter gave a heavy growth of B. proteus, E. coli, and alpha-streptococcus fecalis. Her tablets proved to be sulfanilamide, and she had a sulfanilamide blood concentration of 3.8 mm. per 100 cc., (although she denied having taken the drug for six months). Cultures of the blood and urine were sterile. X-ray studies revealed no evidence of osteomyelitis, and the lungs were clear. There were no abnormalities in the blood chemistry, aside from evidence of dehydration and acidosis. A Congo Red test for amyloidosis revealed only 5 per cent absorption of the dye from the blood stream in seventy minutes. An interesting finding was a positive agglutination by the patient's serum of B. proteus X-2, to a dilution of 1:640. There was no agglutination of B. proteus X-19.

The dehydration, acidosis, and vomiting were rapidly relieved by appropriate therapy; the cyanosis soon disappeared. One morning, the day after close questioning about sulfanilamide, the patient's bottle of tablets was found empty. The tablets had been distributed through her powder box. Nevertheless the patient continued to make a show of being cooperative, while manifesting indifference toward her illness. We expressed great desire to see one of her attacks. She

stated that she then had some joint pains, and that an attack was due. When none appeared she repeatedly asked for a few hours' leave-of-absence, promising to return as soon as chills began. She was not granted leave-of-absence. Psychiatric examination revealed very little, except that she and her husband, though supposedly happy, had not lived together for twenty years.

After eight days on the ward, when confronted with the situation and the evidence, the patient emphatically denied everything and departed within the next few hours. We have been able to learn nothing of her course since then.

The distribution of the abscesses, the discovery of the ampule containing material infected with B. proteus, the agglutination of B. proteus X-2 by the patient's serum, the cyanosis presumably due to self-medication with sulfanilamide, and the curious course of the illness over a period of two years afford circumstantial evidence to stamp the patient as a malingerer. Since adequate rapport was never attained, we have no idea of the basic psychopathology. We may presume that the patient originally had pyuria, possibly pyelitis; and that she became a malingerer after the subsidence of this illness.

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LOSS OF VIRULENCE OF TREPONEMA PALLIDUM IN CITRATED BLOOD AT 5°C.

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Submitted for publication February 26, 1941

Instances of transfusion syphilis have been recorded in which the donor was apparently in the incubation period of the disease, without lesions or a positive serologic test of the blood, these developing only days or weeks after the recipient received the blood (1, 2, 3). Such occasional accidents are impossible to prevent by the usual clinical and serologic safeguards, when direct or immediate indirect transfusion is employed.

The use of fresh, whole or citrated blood for transfusions is, however, being rapidly replaced in most large hospitals by the blood bank, in which citrated blood is stored at icebox temperature for periods ranging from 1 to 21 days before its use. Under these conditions it is essential to know the survival time of *T. pallidum* in blood so stored, in order to determine whether the risk of transfusion syphilis may be still further reduced by storage for an arbitrary time period.

The following experiment was planned to determine the survival time of *T. pallidum* in rabbit testis emulsion, when mixed, in large amounts, with citrated rabbit blood, kept at blood bank temperature, 3–5°C. (4).

EXPERIMENTAL METHOD

Into each of six small sterile test tubes was placed 0.75 cc. of the supernatant portion of a centrifuged fresh saline suspension of syphilitic rabbit testis, containing between 25 and 50 actively motile spirochetes (Nichols Strain of T. pallidum) per oil-immersion darkfield. Each tube then received 4.0 cc. of freshly drawn, warm blood from a normal rabbit, citrated by adding 1.0 cc. of 5.0 per cent sodium citrate solution for each 9.0 cc. of blood. The tubes were immediately closed with rubber stoppers to produce a partial fall of air pressure as the tubes cooled, simulating blood bank conditions (4), and were placed in an icebox at 3–5°C.

As controls, two rabbits were inoculated into each testis with 0.1 cc. of the

[1] Parke-Davis Fellow in Medicine.

blood-spirochete mixture from one of the tubes, and two animals with 0.1 cc. of the original spirochete emulsion, at the time the tubes were placed in the icebox.

At intervals of 24, 48, 72, 96, and 168 hours, and 10 and 14 days, 1.0 cc. samples were withdrawn from successive tubes of blood and injected into each testis of successive pairs of normal rabbits. At each sampling, the supernatant serum was examined by darkfield microscopy, and 5–6 spirochetes were seen in each field, though these were motile only on the day of setting up the tubes.

When palpable testicular lesions appeared they were either aspirated or removed,

TABLE I

Results of Intratesticular Inoculation of Normal Rabbits With Suspensions of T. pallidum Kept Different Lengths of Time in Citrated Rabbit Blood at 5°C.

RABBIT INOCULATION NUMBER	INOCULUM	TIME IN ICEBOX	SYPHILOMA DETECTED—DAYS AFTER INOCULATION	RESULTS OF MODE AND TESTICULAR TRANSFER
5953	Testicular emulsion without blood	0	+18	Not done
5973	Testicular emulsion without blood	0	+18	Not done
5976	Testicular emulsion with blood	0	+22	Not done
5990	Testicular emulsion with blood	0	+22	Not done
5965	Testicular emulsion with blood	24 hours	+48	Not done
5966	Testicular emulsion with blood	48 hours	+48	Not done
5970	Testicular emulsion with blood	48 hours	+48	Not done
5971	Testicular emulsion with blood	72 hours	+50	Not done
5972	Testicular emulsion with blood	72 hours	+50	Not done
5955	Testicular emulsion with blood	96 hours	0	Negative
5974	Testicular emulsion with blood	168 hours	0	Negative
5975	Testicular emulsion with blood	168 hours	0	Negative
5959	Testicular emulsion with blood	10 days	0	Negative
5962	Testicular emulsion with blood	10 days	0	Negative
5967	Testicular emulsion with blood	14 days	0	Negative
5968	Testicular emulsion with blood	14 days	0	Negative

and the aspirated serum or ground tissue was examined by darkfield for the presence of spirochetes. Animals without demonstrable lesions were examined weekly for 6 months. At 3½ months, lymphnode and testicular transfers were made from them to normal rabbits, which were observed for 2 months for the appearance of lesions of syphilis.

RESULTS (*See Table I*)

The control rabbits which received the original testicular emulsion developed syphilomas within 18 days after inoculation. Those inoculated from the fresh blood-spirochete mixture showed similar lesions at 22 days.

The rabbits inoculated with the blood-spirochete mixture kept at icebox temperature for 24 and for 48 hours showed syphilitic lesions in 48 days (except one which died), and the animals inoculated with the 72-hour mixture developed chancres in 50 days. In none of the rabbits inoculated later than 72 hours after the start of the experiment, (i. e. at 96 and 168 hours, and at 10 and 14 days) did lesions develop, and the lymphnode and testicular transfers were negative.

DISCUSSION

The accuracy of the foregoing determination of survival time may possibly be conditioned by the fact (unpublished observation by Eagle (5)) that the addition of testicular tissue to a mixture of serum and *T. pallidum* increases the longevity of the organisms if the mixture is kept anaerobically, but may either prolong or shorten the survival time if the preparation is aerobic. If too much tissue is present in aerobic preparations oxidation may result in increasing the acidity of the medium beyond the tolerance of the spirochetes.

In the present experiment it is probable that at least partially anaerobic conditions existed during the icebox storage period. This is indicated by the fact that the blood darkened, i.e. its hemoglobin was reduced, within about a day after filling and stoppering the tubes. The assumption is that cellular metabolism consumed the atmospheric oxygen in the tubes, though this has not been proved.

The partial anaerobiosis, as well as the presence of buffering substances in the blood, makes it unlikely that any important change of acidity took place. If the testicular tissue had any effect upon the longevity of the spirochetes in this experiment, it was probably in the direction of preserving rather than of killing them. This assumption is partly supported by the findings of Turner and Diseker (6), that in human blood containing a much smaller inoculum than here, and therefore less testicular tissue, *T. pallidum* apparently did not survive as long as 72 hours.

SUMMARY AND CONCLUSION

It has been demonstrated that, in fairly heavy suspension in citrated rabbit blood at 5°C., *T. pallidum* may survive for as long as 72 hours. Survival for 96 hours was not demonstrated.

It is therefore concluded that there is definite risk of transmitting syphilis to the recipient of blood from patients with early syphilis if the blood has been preserved for 72 hours or less in the blood bank. Though this risk probably diminishes rapidly after 96 hours, it would still be unwise to use the blood from persons with known early syphilis, since conclusions cannot be safely carried from one species of animal to another.

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PROCEEDINGS OF THE MEETING OF THE JOHNS HOPKINS MEDICAL SOCIETY

Held in the Hurd Memorial Hall, March 10, 1941

The President of the Society, Dr. Warfield M. Firor, presided. Abstracts of the papers and discussions follow:

Studies on Hypersensitivity in the Human to the Poison Ivy Plant. (*Colored Motion Pictures.*) By Edmund L. Keeney and Stewart Sunday. (Department of Medicine.)

This past year the City of Baltimore established the first Municipal Poison Ivy Clinic. The primary purpose of this clinic was to find suitable methods to decrease compensation disability for poison ivy dermatitis amongst the city employees. Three hundred and twenty six (326) men reported to the clinic. One hundred and forty two (142), that is 44 per cent, gave a positive history of poison ivy dermatitis. In this positive history group, 13 per cent gave a history of having had one or more of the common allergic diseases and 16 per cent gave a positive family history of poison ivy dermatitis. In the negative poison ivy history group only 2 per cent gave a history of having had one or more of the allergic diseases, and only 5 per cent gave a positive family history of poison ivy dermatitis.

Motion Pictures

Part I: Demonstrates the attempt made to discover a substance that would block the experimental poison ivy reaction. Ferric chloride solution, potassium permanganate solution, sodium perborate in vanishing cream, vanishing cream, manganese chloride solution, extract of jewelweed, and rancid butter were used. Ferric chloride solution alone possessed the ability to block the poison ivy reaction.

Part II: Demonstrates the methods employed in determining the reacting ability of the skin at different sites on the body in hypersensitive individuals. The skin of the abdomen and of the back possessed a reacting ability that was better coordinated with the clinical findings and the history (of a hypersensitive individual) than the skin at other sites on the body.

Part III: Demonstrates that a positive patch test produces a refractory period in the state of hypersensitivity which persists for at least 6 to 8 weeks. The possibility that this observation might lead to a simple method of providing protection against poison ivy dermatitis is intriguing.

Part IV: Demonstrates the absolute effectiveness of a 10 per cent ointment of ferric chloride and the partial effectiveness of a 10 per cent ointment of ferrous sulphate in blocking the experimental poison ivy reaction.

From the results of these experimental studies the 10 per cent ointment of ferric chloride should clinically protect against poison ivy dermatitis if it is applied before contact with the poison ivy plant occurs.

DISCUSSION

Dr. Lloyd W. Ketron said that Dr. Keeney had given a very dramatic presentation of his experimental results and that it was to be hoped that the practical application would be as successful. There is a good deal of contradictory literature on the subject which certainly needs clarification. It is well known that the patch test cannot always be depended upon as an exact index of skin sensitivity. There are several factors which might influence the reaction; for example, it is possible that the hydrogen ion concentration of the skin which varies not only in different individuals but in different locations on the same person, and even from time to time in the same location, might affect the degree of reaction. The response to the test may also be affected by mechanical factors. If the test substance is placed beneath the belt or in another location that might be subject to pressure from some article of clothing, or the patient's activities, it is quite apparent that the reaction might definitely be accentuated.

Struma Ovarii: Report of Two Cases. By J. DONALD WOODRUFF. (Department of Gynecology.)

A brief summary of the history and literature concerning *struma ovarii* was presented, and controversial points as to definition and classification were considered.

The histories of new cases were presented in detail. In the first case, the ovarian tumor was large, weighing 1690 grams, and was composed largely of thyroid tissue. The major portion of this tumor showed a solid, trabecular, adenomatous change which seemed to be developing directly from the thyroid portion. Deep x-ray therapy was given post operatively with good results. The patient later developed a benign enlargement of the thyroid of the neck and this was removed. It was suggested that the latter struma might have been due to a compensatory hypertrophy.

In the second case, the patient had a subtotal thyroidectomy performed because of diffuse enlargement of the thyroid of the neck, associated with symptoms of hyperthyroidism. Postoperatively the symptoms retrogressed, and the basal metabolic rate fell although the latter was still elevated ten days postoperatively. Four months later the removal of a pelvic tumor was followed by the development of mild myxoedema. The pelvic tumor was made up of a myomatous uterus and bilateral dermoid cysts, one of which contained thyroid tissue. In this thyroid there was definite microscopic evidence of hyperplasia. The development of myxoedema following the pelvic operation in this case is fairly definite evidence of activity of the ovarian thyroid.

Q Fever Pneumonitis. By R. E. DYER. (Chief, Division of Infectious Diseases, United States Public Health Service.)

In 1937, Australian workers described, under the name Q fever, a disease occurring among abattoir workers in Queensland. They began their investigations in 1935 and have continued them to date. The salient features of this disease as described by the Australians are: Fairly acute onset, prostration, headache, insomnia, continuous fever lasting a few days to three weeks, repeated chills and in some cases profuse sweating at night. In the clinical descriptions of the first nine cases, some respiratory involvement was noted in four. Apparently no x-ray plates of the lungs have been made. The causative agent of this disease was established in guinea pigs by blood inoculation and identified as a rickettsia and named *R. burneti*. This rickettsia differs from the well-recognized rickettsiae in that (1) it is filterable, (2) infection with it does not produce agglutinins for any of the known Proteus X strains, and (3) the epidemiology, as far as described, is not that of an arthropod borne disease although an animal reservoir has been found in the bandicoot and naturally infected ticks (Haemaphysalis humorosa) have been discovered.

For diagnosis, reliance is placed on the agglutination of suspension of *R. burneti*, dilutions as low as 1:10 being considered diagnostic.

Little apparently is known of the epidemiology of the disease. Most of the located cases have occurred among abattoir workers with a few among foresters and farmers.

In the same year in which Australian work was begun, an infectious agent was isolated from ticks in Montana. This agent was rickettsia-like and since it had been recovered from ticks, there was little hesitation in classing it as a rickettsia although, like *R. burneti*, it also passed through bacterial filters. The Montana rickettsia was named *R. diaporica*. An accidental laboratory infection demonstrated that *R. diaporica* was infectious for man. Subsequent comparisons, cultural, immunological, and serological, have shown that *R. burneti* and *R. diaporica* are very closely related if not identical.

In the spring of 1940, fifteen cases of an atypical pneumonia occurred in the Infectious Diseases building at the National Institute of Health. These cases were shown to be "Q" fever. Since studies were being made on this disease in animals in the same building, the possibility of "laboratory infections" could not be ruled out although there was nothing in the epidemiology which suggested connection of these cases with the Q fever study unit in the same building.

The cases at the National Institute of Health had, clinically, a close similarity to the atypical pneumonias described by Bowen, Allen, Bock, Reimann, Smiley, Kneeland, and Longcope. From similar cases in New York State, Weir and Horsfall have reported the isolation of a virus.

Attempts have been made to isolate the Q fever virus or rickettsia from similar outbreaks of atypical pneumonias at two institutions in the past few months, so far without success.

It appears that Q fever does cause a pneumonitis. Whether this will explain

any of the cases of atypical pneumonias which have occurred in the past few years is still an open question.

DISCUSSION

Dr. Warfield T. Longcope said that he had examined Dr. Dyer's x-ray plates with him and that he could see nothing in the x-ray shadows in the lungs which would allow one to distinguish between the type of pneumonitis which Dr. Dyer was discussing and the type of pulmonary lesions which occurred in patients with so-called "variety X" pneumonia. This year Dr. Thomas McP. Brown had had an opportunity to study two cases which had been classified in the clinic here as "variety X" pneumonia. In neither of the two cases, so far as the studies have gone at present, was Dr. Brown able to discover any evidence that the disease was due to the virus of Q fever.

At the present time, there are apparently several forms of pneumonia which present a similar clinical picture but in which the disease is due to different etiological agents. For example, in 1935, Goodpasture described an epidemic in infants in which pathological studies showed inclusion bodies in the cells lining the alveolar spaces of the lungs. Adams has just recently reported another group of similar cases. Pinkerton reported one or two cases in St. Louis in which an acute pulmonary disease of the type under discussion was found to be associated with the occurrence of toxoplasma in the lungs. Toxoplasma could not be found in the lungs of the fatal cases which occurred in this clinic. Dr. Longcope said that in one of his cases, Dr. Frank B. Kindell had tried unsuccessfully to isolate a virus by inoculating mice and ferrets. In fact, it seemed to be generally agreed that ferrets cannot be infected with the agent which causes "variety X" pneumonia. Dr. Dyer's cases of atypical pneumonia seem to represent still another type of disease.

Dr. Thomas McP. Brown said that after he had heard about Dr. Dyer's work, he had had an opportunity to obtain material from two cases of atypical pneumonia. One of these patients was very ill, and several samples of blood had been used for animal inoculation during the acute active stage of the disease. The blood of these patients had been injected into guinea pigs and none of the inoculated animals developed fever. Material from these guinea pigs had been injected into other guinea pigs, again with negative results. Whole blood had also been injected intraperitoneally into mice, and sputum had been inoculated intranasally in mice. The results of these experiments were also negative. Dr. Brown said that he would like to ask Dr. Dyer to amplify his statement concerning the passage of the rickettsia from guinea pigs to mice. Dr. Dyer had said that the rickettsia could be more readily found in the spleens of mice which had been inoculated with the spleens of infected guinea pigs.

Dr. Longcope asked Dr. Dyer whether the long incubation period of the atypical pneumonias, which appeared to be 14 to 21 days, might not make it difficult to draw any conclusions concerning contact spread of the disease, especially when one

was dealing with groups of individuals confined in a small area such as a boarding school.

Dr. Dyer said that in answering Dr. Longcope's question, he quite agreed that it was difficult to draw any conclusions concerning the mode of spread of the disease in a school but he thought that it was of significance that in the cases which occurred in the National Institute of Health, there were forty-four home contacts, none of whom developed the disease.

In answer to Dr. Brown's question, Dr. Dyer said that it was very difficult to detect the rickettsiae in the liver or spleen of guinea pigs but that when the agent was passed from guinea pigs to mice and then carried on in successive mouse transfers the chance of detecting rickettsiae in the mouse spleens improved with each transfer.

Dr. Arnold R. Rich asked whether any of the individuals in the National Institute of Health had developed positive agglutinins, without developing the disease.

Dr. Dyer said that he could not give exact figures without looking over the records but, as he recalled the figures, they were somewhat as follows: ten of the fifteen cases with the clinical disease showed agglutinins (three sera were not tested); four of ten persons working in the rickettsial unit had positive agglutinins without having clinical disease; while only two of a random sample of twenty of the remaining one-hundred and twenty-five individuals in the Institute had agglutinins.

BOOK REVIEWS

(These reviews represent the individual opinions of the reviewers and not necessarily those of the members of the Editorial Board of this Journal.)

Methods for Diagnostic Bacteriology. By ISABELLE G. SCHAUB and M. KATHLEEN FOLEY. 313 pp. $3.00. *C. V. Mosby Company, St. Louis, 1940.*

This small volume, only half the length the 313 pages mentioned in the listing would lead one to expect, contains an abundance of information set forth in so explicit and yet simple a manner that with its help the veriest tyro should be able to manage even fairly complicated routines.

The authors know whereof they write. For a number of years they have been in charge of, respectively, the autopsy and the medical diagnostic bacteriological laboratories at The Johns Hopkins Hospital. Part of their work has been to instruct internes and students in routine bacteriology. They, therefore, recognize the points at which the novice is likely to feel baffled.

The book should be valuable to those with more experience also. Several of the techniques described are by no means common. The authors are not the sort to let the grass of tradition impede their progress, and they have had the advantage of frequent contact with the ingenious mind of Dr. J. Howard Brown. Then, realizing that others may have their own pet methods, they have left one side of each page blank for notes. While this format is somewhat annoying to a person who is trying to follow a given procedure, it should prove stimulating to the enterprising worker. Finally, praise should be given for the excellent compendium of stains, culture media, and reagents for special tests which appears at the end of the book.

E. A. B.

Graduate Medical Education. Report of the Commission on Graduate Medical Education. 304 pp. *University of Chicago Press, Chicago, 1940.*

This volume is the report of a study conducted by the Commission on Graduate Medical Education which was organized under the auspices of the Advisory Board for Medical Specialties. The Commission itself consisted of twenty persons well known in the field of American medical education, and enjoyed the support of several philanthropic agencies and organizations. The actual study itself was carried out by Dr. Robin C. Buerki, who was given leave of absence from his post as Administrator of the Wisconsin General Hospital, for that purpose.

The report, as the preface states, is not so much a factual document as it is an attempt to create standards by bringing together "the best medical and educational ideals and philosophies and to synthesize these into a series of consistent workable principles."

Most of the report is given over to a discussion of the internship and the resi-

dency viewed as opportunities for continuing education in medicine. Rather less space is devoted to the education of the practitioner after he has finished his hospital training. One chapter is devoted to the specialty boards and there is an instructive chapter contributed by Dean Rappleye of the College of Physicians and Surgeons of Columbia University on Postgraduate Medical Education in Great Britain followed by appendices giving factual information concerning internships and residencies available in the United States, and various plans being carried out in the country in an endeavor to provide postgraduate medical education for those in practice.

Throughout the report the note is sounded of the necessity of increasing the value of the period of hospital training as an educational experiment. With this thesis no sane person would quarrel, but there is perhaps some room for doubt as to the wisdom of some of the suggestions for bringing this result about which are put forth in the report, as, for example, the appointment, by the hospitals, of officials to serve as "educational directors", who will be responsible for organizing a more or less formal system of instruction for house officers and seeing that it operates smoothly. One wishes that the report had laid a little more stress on the fact that hospital training must of necessity be much more in the nature of apprenticeship training than of systematic didactic instruction. As in all apprentice systems its value will rest primarily upon the character and ability of the master under whom the apprentice works. No carefully worked out schedule of formal exercises for house officers will ever replace the precious opportunity to work under a brilliant master of his craft and observe his methods at first hand.

A. M. C.

Physiology of the Fetus. By WILLIAM FREDERICK WINDLE. 249 pp. Illus. $4.50. *W. B. Saunders Company, Philadelphia and London, 1940.*

This volume summarizes in succinct and scholarly form our modern knowledge of the physiology of the fetus. Since no general summary of this subject has appeared since the publication of Wilhelm Preyer's classic, *Specielle Physiologie des Embryo*, in 1885, Dr. Windle's book is most welcome. The author is Professor of Microscopic Anatomy in Northwestern University Medical School and having himself worked long and with distinction on many phases of fetal physiology, speaks with intimate familiarity of the problems concerned.

The book deals primarily, of course, with the genesis of function in the various systems of the body and the extent to which functional activity is exhibited at successive periods of embryonic life. Thus, initiation of the fetal heart beat, the development of the circulation, the question of intra-uterine respiration, fetal swallowing, gastro-intestinal movements, the origin of urinary secretion, the genesis of the nervous system and the prenatal activity of the fetal endocrine glands are all discussed in detail. A large amount of literature bearing on these topics is reviewed and the evidence analyzed critically to the end that a valid conclusion can be reached.

Although Dr. Windle's monograph deals chiefly with the functional activity of embryonic organs, it touches upon many topics of vital concern to the newborn.

This applies particularly to the discussion of the moot question of intra-uterine respiration, a question so important that our whole concept of respiratory activity and respiratory pathology in the early neonatal period, hangs upon it. This book, therefore, should be of interest not only to the embryologist and physiologist, but to the obstetrician, pediatrician and pathologist as well.

N. J. E.

Management of Obstetric Difficulties. By PAUL TITUS. 2nd ed. 968 pp. Illus. $10.00. *C. V. Mosby Company, St. Louis, 1940.*

This second edition of Dr. Titus' well-known work incorporates recent advances in the relief of female sterility, the use of sulfanilamide in puerperal sepsis and pyelitis, a detailed account of x-ray pelvimetry, technical advances in the care of the toxemias and anemias of pregnancy and current improvements in obstetric analgesia and anesthesia. There are seventy-five new illustrations which represent a gratifying addition. As was true of the first edition, the subject matter is limited to the practical aspects of obstetric emergencies, the book being in no wise a complete text-book. It will doubtless continue to serve practitioners, however, as a useful and authoritative variant to the standard text-books when practical problems are at issue.

N. J. E.

Attaining Womanhood. By GEORGE W. CORNER. 95 pp. $1.00. *Harper & Brothers, New York & London, 1939.*

It is the purpose of this small and attractive volume "to provide intelligent girls of high school age with a scientific account of sex and human reproduction". The first half of the book deals with the essentials of anatomy and physiology; this is written in simple, lucid form and gains much both in interest and clarity by frequent correlation of human phenomena with those of the plant and animal kingdoms. The remainder of the volume is devoted to a consideration of the sex problems which the girl between fifteen and eighteen is likely to encounter. The subject matter is presented from a biological point of view, the fact being stressed that a wholesome sex life is simply "good biology". The book is the best of its kind which the reviewer has seen and can be recommended without reservation to parents of adolescent daughters.

N. J. E.

Pathological Histology. By ROBERTSON F. OGILVIE. 332 pp. Illus. $8.50. *Williams & Wilkins Co., Baltimore, 1940.*

The scope of this volume is limited. It is not an original work, and consists essentially of concise descriptions of the microscopical lesions which occur in the diseases most commonly seen in Great Britain. There is little space for discussion, and there are no references to the literature.

The special feature of the book is the presentation of 220 very good colored photomicrographs. The author states in the preface that the volume is designed to act as a companion to a standard text-book of Pathology.

S. S. B.